ARTERIAL EMBOLIZATION IN
GASTROINTESTINAL BLEEDING

Taina Nykänen

ACADEMIC DISSERTATION

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ABSTRACT

**Background.** Gastrointestinal bleeding is a common surgical emergency resulting in significant morbidity and mortality especially in moribund patients receiving anticoagulant medication. Its initial management comprises fluid resuscitation, red blood cell transfusions, and the optimization of hemostasis with medication and additional blood products. The first line intervention in most cases is therapeutic endoscopy. When endoscopy fails, the traditional second line treatment is surgery. Emergency surgery is associated with high morbidity and mortality. As a less invasive alternative, transcatheter arterial embolization (TAE) has become routine practice. The thesis aimed at studying the safety, efficacy and feasibility of TAE in the treatment of gastrointestinal bleeding.

**Materials and Methods.** The thesis comprises four original studies reviewing TAE in the management of bleeding pancreatic pseudoaneurysms (Study I), bleeding gastric and duodenal ulcers (Study II), lower gastrointestinal bleeding (Study III), and spontaneous hepatic tumor hemorrhage (Study IV). Studies I, II and IV are retrospective studies. Study II is a retrospective case-control study comparing TAE and surgery.

The study included all patients undergoing angiography and embolization attempt for gastrointestinal bleeding in the Helsinki University Hospital during 2004-2017. Studied outcomes included the 30-day rebleeding, complication and mortality rates, need for blood transfusions, the durations of intensive care unit and hospital admissions, the incidence of delayed rebleeding and complications, and the analysis of overall survival.

**Results.** In Study I, TAE was technically feasible in 100% of patients and controlled the bleeding initially in 85%. The 30-day complication and mortality rates were 31% and 3%, respectively. Occurring in 50% of patients after splenic artery embolization, the most common complication was splenic infarction.

In Study II, TAE was feasible in 92% and surgery in 100% of patients. The 30-day complication rate was lower after TAE than surgery (38% vs. 67%, \( P = 0.018 \)). The 30-day rebleeding rates (25% vs. 16%, \( P = 0.641 \)) and mortality rates (13% vs. 26%, \( P = 0.347 \)) did not differ between TAE and surgery.

In Study III, TAE was feasible in 96% of patients and controlled the bleeding initially in 74%. The 30-day complication rate was 36%. The most common complication was bowel ischemia occurring in 19% of patients and requiring surgical management in six patients (11%). The 30-day mortality rate was 6%.

In Study IV, TAE was feasible in 92% of patients and controlled the bleeding in 84%. The 30-day complication and mortality rates were 55% and
33%, respectively. In-hospital mortality was higher in cirrhotic than non-cirrhotic patients (55% vs. 7%, $P < 0.001$), whereas patients with bleeding hepatic metastases, but no cirrhosis, had an in-hospital mortality of 0%.

**Conclusions.** TAE is an effective method in controlling gastrointestinal bleeding. Ischemic complications remain a concern especially in lower gastrointestinal hemorrhage. Although only a small percentage of bleeding patients require TAE, it has established its role in the multidisciplinary management of gastrointestinal bleeding and should be the preferred method over surgery in most non-traumatic bleeding emergencies.
TIIVISTELMÄ


**Tulokset.** Ensimmäisessä osatyössä embolisaatio onnistui teknisesti 100%:lle ja tyrehdytti vuodon ensiyrittämällä 85%:lla potilaista. Komplikaatiota eli pernavaihto, joka todettiin pernavaltimon embolisaation jälkeen joka toisella. Kuolleisuus (≤ 30 vrk) oli 3%.

Toisessa osatyössä embolisaatio onnistui teknisesti 92%:lle potilaista ja leikkaushoito 100%:lle. Angioembolisaatioon liittyi leikkaushoitoa vähemmän komplikaatiota (38% vs. 67%, P = 0,018). Embolisaation ja leikkaushoidon välillä ei ollut eroa uusintavuodoissa (25% vs. 16%, P = 0,641) tai kuolleisuudessa (13% vs. 26%, P = 0,347) 30 vuorokauden sisällä toimenpiteestä.

Kolmannessa osatyössä embolisaatio onnistui teknisesti 92%:lle potilaista ja tyrehdytti vuodon ensiyrittämällä 74%:ltä. Embolisaationjälkeisiä komplikaatiot ilmaantui 36%:lle. Yleisin komplikaatio oli suoliston
iskemia, joka todettiin 10:llä potilaalla (19%). Iskemia johti leikkaushoitoon kuudella (11%). Kuolleisuus (≤ 30 vrk) oli 6%.

Neljännessä osatyössä embolisaatio onnistui teknisesti 92%:lle potilaista ja tyrehdytti vuodon 84%:ltä. Kolmenkymmenen vuorokauden sisällä toimenpiteestä 55%:lle potilaista ilmaantui komplikaatioita ja 33% kuoli. Sairaalakuolleisuus oli korkeampi kirroosipotilailla kuin ei-kirrootikoilla (55% vs. 7%, \( P < 0,001 \)). Vuotaneen maksametastaasin takia hoidetuilla potilailla sairaalakuolleisuus oli 0%.

**Päätelmät.** Angioembolisaatio on tehokas menetelmä ruoansulatuskanavan verenguotojen hoidossa. Iskeemiset komplikaatiot ovat riski erityisesti ruoansulatuskanavan alaosan verenguotojen embolisaatioissa. Vaikka vain pieni osa vuotopotilaista tarvitsee angioembolisaatiota, on embolisaatio olennainen osa ruoansulatuskanavan verenguotojen moniammatillista hoitoa ja sen tulisi olla ensisijainen menetelmä kirurgiaan verrattuna valtaosassa ei-traumaattisia vatsan alueen vuotoja.
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


II Nykänen T, Peltola E, Kylänpää L, Udd M. Bleeding gastric and duodenal ulcers: Case-control study comparing angioembolization and surgery. *Scand J Gastroenterol.* 2017: 52; 523-530


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<table>
<thead>
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<th>Abbreviation</th>
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<tr>
<td>AFP</td>
<td>Alfa-Fetoprotein</td>
</tr>
<tr>
<td>AVP</td>
<td>Amplatzer Vascular Plug</td>
</tr>
<tr>
<td>CIN</td>
<td>Contrast-Induced Nephropathy</td>
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<tr>
<td>CTA</td>
<td>Computerized Tomography Angiography</td>
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<tr>
<td>CT</td>
<td>Computerized Tomography</td>
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<tr>
<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
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<td>DSA</td>
<td>Digital Subtraction Angiography</td>
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<tr>
<td>ERCP</td>
<td>Endoscopic Retrograde Cholangiopancreatography</td>
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<tr>
<td>EVOH</td>
<td>Ethylene Vinyl Alcohol Copolymer</td>
</tr>
<tr>
<td>FDA</td>
<td>The United States Food and Drug Administration</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
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<td>GDA</td>
<td>Gastroduodenal Artery</td>
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<tr>
<td>HCA</td>
<td>Hepatocellular Adenoma</td>
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<tr>
<td>HCC</td>
<td>Hepatocellular Carcinoma</td>
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<tr>
<td>IMA</td>
<td>Inferior Mesenteric Artery</td>
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<tr>
<td>ICM</td>
<td>Iodinated Contrast Medium</td>
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<tr>
<td>ICRP</td>
<td>The International Commission on Radiological Protection</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>LGA</td>
<td>Left Gastric Artery</td>
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<td>LGIB</td>
<td>Lower Gastrointestinal Bleeding</td>
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<tr>
<td>MRA</td>
<td>Magnetic Resonance Angiography</td>
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<td>MRE</td>
<td>Magnetic Resonance Enterography</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NBCA</td>
<td>N-Butyl Cyanoacrylate</td>
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<tr>
<td>PTA</td>
<td>Polyethylene terephthalate</td>
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<tr>
<td>PTFA</td>
<td>Polytetrafluoroethylene</td>
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<td>PVA</td>
<td>Polyvinyl Alcohol</td>
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<td>RBC</td>
<td>Red Blood Cell</td>
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<td>SMA</td>
<td>Superior Mesenteric Artery</td>
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<td>TACE</td>
<td>Transcatheter Arterial Chemoembolization</td>
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<td>TAE</td>
<td>Transcatheter Arterial Embolization</td>
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<td>TAGM</td>
<td>Trisacryl Gelatin Microsphere</td>
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<td>UGIB</td>
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Introduction

1 INTRODUCTION

Gastrointestinal bleeding is a frequently encountered problem in surgical emergency units. Depending on its severity and origin in the gastrointestinal tract, it may present itself as anemia, hematemesis, melena or hematochezia. Abdominal pain and tenderness without visible blood are common in intraperitoneal and intraparenchymal bleeding. The signs of hemodynamic compromise, such as collapse or hemodynamic shock, are often present and usually signify active bleeding.

Non-variceal upper gastrointestinal bleeding (UGIB) originates in the stomach or duodenum. Its symptoms include hematemesis and melena. Hematochezia may be present if bleeding is profuse. The most common underlying etiology is peptic ulcer disease, although the introduction of proton pump inhibitors and the eradication of Helicobacter pylori have changed its epidemiology [1-3]. The incidence of peptic ulcer disease in Finland decreased from 121 to 79/100,000 between 2000-2002 and 2006-2008 [4]. During the same period, the incidence of complicated peptic ulcers decreased from 53 to 37/100,000. The effective conservative management has nearly eliminated the need for elective peptic ulcer surgery [5]. Nonetheless, complicated peptic ulcers remain a problem and warrant emergency interventions. Additional hemostatic procedures are necessary in 3.6-14% of patients after failed endoscopic hemostasis [6-9]. Short-term mortality remains in 4.4-5.6% [10]. Risk groups include elderly patients with multiple comorbidities and anticoagulant medication [11,12].

Lower gastrointestinal bleeding (LGIB) refers to hemorrhage originating in the bowel distal to the ligament of Treitz. Small intestinal bleeding or bleeding from the proximal colon may present as melena. Bright red blood with blood clots is usually a sign of bleeding from the left-sided colon or rectum. Diverticular disease is the most common etiology accounting for up to 40% of LGIB [13]. Other etiologies include benign anorectal causes, post-polypectomy bleeding, tumors, colitis, and vascular ectasia. Some 80% of bleeding episodes resolve spontaneously, the remaining requiring hemostatic interventions [13]. LGIB has an incidence of 20-30 per 100,000 and a mortality of 5% [14]. Short-term mortality is usually related to exacerbating underlying comorbidities in elderly patients rather than to severe bleeding per se [15].

Visceral artery aneurysms and pseudoaneurysms involve the coeliac artery, superior mesenteric artery (SMA), inferior mesenteric artery (IMA), and their branches. In autopsy series, they occur in up to 2% of population [16]. They are often asymptomatic incidental findings in cross sectional imaging but can also present as life-threatening rupture and bleeding [16]. Aneurysms, or true aneurysms, involve all three layers of the arterial wall and have various underlying etiologies such as arteriosclerosis, connective tissue
disorders and vasculitides [17]. Inflammatory, iatrogenic, and infectious processes cause pseudoaneurysms, or false aneurysms. They involve only the outermost layer of the arterial wall and are, thus, more prone to rupture [17,18]. Mortality from rupture ranges from 25-100% depending on the size and location of the aneurysm [17]. Pancreatic pseudoaneurysms are a rare complication of pancreatitis occurring in 1-5% of patients [19-21]. They arise in nearby visceral arteries coming into contact with eroding pancreatic juices and chronic inflammation. Pancreatic pseudoaneurysms can cause intraperitoneal bleeding, bleeding limited to the pseudocyst, or bleeding from the duodenal papilla resulting in hematemeses or melena. If left untreated, they have a mortality of up to 90-100% [22].

Spontaneous rupture and hemorrhage of a hepatic tumor is a rare surgical emergency. Its incidence in western countries is 1% [23]. The most common underlying etiology is hepatocellular carcinoma (HCC) [24]. Less frequent etiologies include other malignant neoplasms (liver metastases, angiosarcomas, hepatoblastomas) and benign tumors (hepatocellular adenomas (HCAs), hemangiomas, angiolipomas, focal nodular hyperplasias). Tumor rupture may cause intrahepatic hematomas, intraperitoneal bleeding, or hemobilia when the tumor erodes the biliary ducts [23]. Treatment is often challenging, especially in cirrhotic patients with HCC and coagulopathy. Survival depends on the underlying tumor etiology. Patients with a malignant tumor and advanced cirrhosis have a high in-hospital mortality ranging from 25 to 100% [25].

At the emergency room the diagnostics and management of gastrointestinal bleeding occur hand in hand. Fluid resuscitation, the discontinuation of anticoagulant medication, and optimizing the clotting status are the first-line stabilizing measures. Red blood cell (RBC) transfusions and other blood products are sometimes necessary. Depending on the etiology, interventional treatment options include therapeutic endoscopy, surgery and transcatheter arterial embolization (TAE). The first-line method in diagnosing and controlling LGIB and UGIB is endoscopy [25]. TAE and surgery are alternatives when endoscopic treatment fails, or when it is not feasible like in bleeding pancreatic pseudoaneurysms and in hepatic tumor hemorrhage.

Laparotomy with general anesthesia is often a major physiological insult in a frail bleeding patient. As a less invasive approach, TAE offers an attractive treatment alternative. Ischemic complications and recurrent bleeding are the main concerns after embolization. The aim of this thesis was to study the safety, efficacy and feasibility of transcatheter arterial embolization in the treatment of non-traumatic gastrointestinal bleeding.
2 REVIEW OF THE LITERATURE

2.1 TRANSCATHETER ARTERIAL EMBOLIZATION

2.1.1 BACKGROUND

The first angiographies were performed by surgeons through direct cutdown [26]. Introduction of the Seldinger technique (catheterizing the vascular system through needle access) by the Swedish radiologist Sven Seldinger launched the development of interventional radiology in 1953 [26]. In the beginning, catheter angiographies were used exclusively in diagnostics. Transarterial therapeutic interventions evolved during the 1960’s and 1970’s, the first arterial embolization taking place in the United States in 1971 [27]. Since then, the advancements in imaging techniques, interventional instrumentation and embolic materials have made TAE the first-line intervention over surgery in many bleeding emergencies.

2.1.2 ANGIOGRAPHY

*Digital subtraction angiography* (DSA or “angiography” as referred to in the thesis) is a fluoroscopic method that uses digital subtraction technique to visualize vascular structures in bony and soft tissue environments [28]. To remove underlying and overlying distracting structures, a pre-contrast image is subtracted from images acquired after contrast administration. In the era of modern cross sectional imaging, DSA is used only with the intention of simultaneous intravascular therapeutic intervention. Computerized tomography angiography (CTA) and magnetic resonance angiography (MRA), both non-invasive and readily available imaging methods, have replaced DSA in diagnostic use [29]. The Helsinki University Hospital replaced DSA with CTA in the diagnostics of gastrointestinal bleeding in 2007, which has reduced the amount of nondiagnostic angiographies [30].

To visualize the vasculature, angiography requires *contrast agent*. Low-osmolar *iodinated contrast media* (ICM) are nowadays the preferred contrast media in most intravenous and intra-arterial contrast-enhanced imaging [16]. They are less nephrotoxic and have fewer minor side effects (i.e. pain, heat, nausea, urticaria) than the less expensive traditional high-osmolar iodinated contrast media. *Carbendioxide-enhanced angiography* is an alternative to iodine-enhanced imaging especially in patients with iodine allergy or a high risk for contrast-induced nephropathy [31].
Angiography begins by using the Seldinger technique to gain arterial access through the femoral or brachial artery [29]. After arterial puncture with a Seldinger needle, a guide wire is advanced into the artery through a cannula. The cannula is then removed. A catheter sheath with a dilator is introduced into the artery over the guide wire. The dilator and guide wire are removed and the sheath is left in place to provide arterial access during the procedure. The sheath has a valve that prevents hemorrhage and a side arm that enables catheter flushing and contrast administration.

In selective angiography, specific pre-configured catheters are advanced into target arteries over guide wires [29]. The arteries and the organs supplied by the arteries become visible after contrast injection. Arterial, parenchymal and venous phases are documented. To visualize very small arteries, microcatheters are introduced to the target area to achieve the maximum concentration of contrast in the vasculature. This super-selective technique is necessary when diagnosing small changes e.g. in the mesenteric arteries. Gentle catheter manipulation is important to avoid arterial vasospasm, dissection and dislocation of atherosclerotic plaques [32].

When searching for the bleeding site, the most likely anatomic source should be studied first [16]. In LGIB, the SMA and IMA are the primary targets. In UGIB, the coeliac trunk and SMA are studied first. Angiography has the ability to visualize contrast extravasation when the bleeding rate exceeds 0.5 ml/min [33]. CTA is more sensitive and should always precede invasive angiography in diagnosing the bleeding site [33]. A positive pre-angiography CTA allows targeted catheterization and shorter operating times with less contrast use and radiation exposure. Despite positive CTA, angiography may sometimes remain negative due to intermittent bleeding. To stimulate the bleeding in order to localize the pathology, some advocate provocative measures such as administering vasodilators, heparin or even thrombolytics during the procedure [16]. Bowel peristalsis may also cause artefacts. Administering glucagon is often helpful especially before mesenteric angiograms [16]. The inability to detect venous bleeding remains a serious limitation to arterial angiograms.

2.1.3 ARTERIAL EMBOLIZATION

Transcatheter arterial embolization is an intravascular approach to occlude bleeding arteries and arterial anomalies. It is a common procedure for interventional radiologists. DSA technique facilitates the arterial occlusion by allowing catheter-assisted delivery of the chosen embolic agent to the bleeding site. The embolization of a large artery corresponds the effect of surgical ligation.

Successful embolization requires taking several technical, anatomical and physiological details into consideration. First, one should know whether
sacrificing the target artery is possible without the risk of ischemia to organs distal to the embolized segment. Second, the procedure requires the understanding of hemodynamics of the target vessel and the evaluation of the caliber and length of the arterial segment requiring embolization. Third, a thorough understanding of the purpose of the procedure is vital. If ischemia is a desirable consequence of TAE like in intentional tumor embolization, specific embolic agents are necessary [27,34,35].

Different embolic agents are employed in different clinical situations. As a rule of thumb, the smaller the embolic agent, the bigger the likelihood of end organ ischemia [27]. This is related to collateral vasculature that enters the main feeding artery distally and plays a major role in organ survival in the case of proximal vascular insult. Bigger embolic agents provide proximal embolization, leaving the distal collateral vasculature intact. Smaller embolic agents penetrate deeper into capillaries, occluding also the vital collateral arteries.

The diameter of the target artery is important when choosing the embolic agent. In general, all arteries visible in angiography are large, whereas the small ones are not visible with the resolution of DSA. Methods for large artery embolization in hemorrhage typically include coils and vascular plugs, or gelatin sponge when temporary occlusion is an option [27]. Coils and vascular plugs are oversized by 20-30% in relation to the vessel diameter to prevent distal migration [27]. Too much oversizing can prevent coils from achieving their shape resulting in insufficient occlusion. On the other hand, undersizing may lead to distal embolization and ischemia. Options for small artery embolizations include glue and gelatin powder as well as polyvinyl alcohol particles and acrylic microspheres matched for vessel size.

Embolization technique depends on the indication and anatomy [27]. A common method in visceral bleeding is the sandwich technique, where the bleeding artery is occluded proximally and distally to the bleeding site. Scaffolding embolic material may be useful to acquire dense vascular occlusion. This is possible e.g. by initially deploying a larger and stiffer coil as backstop followed by smaller and softer coils allowing tight occlusion. A scaffold with coils and gelatin sponge, “a coil-gelatin sandwich”, may be helpful in acquiring hemostasis in coagulopathic patients. For visceral artery aneurysms, coil packing of the aneurysm, parent artery occlusion with the sandwich technique and endovascular stenting are all applicable approaches [17].

2.1.4 EMBOLIC AGENTS

Early embolization materials included paraffin, hot contrast, fibrin, glass particles, silk threads and tissue fragments like fascial strips, muscle fibers and blood clots [36,37]. None of these are in use today. Modern embolic
agents offer permanent or temporary vessel occlusion. Depending on the need, various methods exist.

**Metal Occlusion Devices**

*Coils.* Coil embolization was first described in 1975 [37]. Today, coils are one of the most often-employed embolization materials. They are made of steel or platinum and maybe coated with thrombogenic fibers or expandable hydrogel to promote hemostasis [36]. In general, steel coils have a greater radial force than platinum coils [38]. Platinum coils are more flexible and highly radiopaque and also more expensive.

Coils are available in various lengths, diameters, conformability, and configurations including helical, conical, tornado, straight and complex three-dimensional forms [37]. Their sizes vary from 0.008 to 0.052 inches [37]. Multiple coil sizes and shapes allow coil embolization in various sites and indications including visceral artery aneurysms and small and tortuous mesenteric arteries. The latter require the use of microcatheters and microcoils due to the small target vessel caliber [37].

Coils are indicated for permanent vessel occlusion. Mechanical occlusion is only partial, and complete vessel occlusion depends on thrombus formation affected by the coagulation status, vessel flow rate and coil type [37]. Usually thrombosis occurs within five minutes of the coil deployment.

Coil pushers, saline flushing or specific detachment systems facilitate the delivery of coils to the desired location [38]. Pushable coils and injectable coils are the most commonly used. A coil pusher wire or saline flushing deploys the coil from the catheter tip [38]. Injectable coils are quicker but less precise to position than the pushable ones [37]. Injectable and pushable coils are not retrievable once detached. Liquid coils are very soft platinum coils with a diameter of 0.008-0.016 inches. They are also detached with saline flush. Liquid coils can be delivered through tight bends. They have the ability to accommodate in tortuous vessels and flow to a target distal to the catheter tip [37,38]. detachable coils can be recaptured and repositioned through mechanical, electric or hydraulic release mechanisms allowing precise coil positioning. They are rare in routine peripheral embolization procedures [38]. Hydrogel coils are available in pushable and detachable variants. Their hydrogel cover causes the coils to swell manifold after coming into contact with blood. Hydrogel coils provide better mechanical occlusion and are less dependant on thrombus formation [37].

Coils are readily available, relatively inexpensive and user-friendly. Their potential drawbacks include the risks of coil displacement and coil migration especially in high-flow vessels. In the presence of distal vascular network, problems may arise when proximal embolization inhibits distal access [36]. Other problems include vessel dissection, perforation and vessel rupture [37].
Amplatzer vascular plug. The United States Food and Drug Administration (FDA) first approved the Amplatzer Vascular Plug® (AVP) for peripheral vascular embolizations in 2004 [39]. AVPs are made of self-expanding braided Nitinol mesh and indicated for permanent vessel occlusion. They produce the occlusion by reducing flow velocity and inducing clot formation that occurs in about 3-5 minutes in the absence of coagulation disorders [36].

AVPs are easy to use and rapid to deliver. Their recapturing and repositioning for precise deployment is possible [36]. Plug migration and the recanalization of the embolized vessel are rare [39]. The four plug types in the market are available in different lengths up to 18 mm and diameters up to 22 mm. They cover various vascular anatomies and hemodynamics and are the most suitable for relatively straight high-flow vessels of medium and large caliber [38]. In gastrointestinal bleeding, AVPs have been used in splenic and gastroduodenal artery embolizations [39] (Figure 1).

Disadvantages include the dependence on the patient’s ability to form thrombus. Occlusion time is unpredictable also in high-flow situations and in vessels with large diameter [39]. Depending on the plug type, the average occlusion times e.g. in the splenic artery may vary between 10-25 minutes, [39]. AVPs do not allow distal embolizations and may be technically challenging to deploy in tortuous vessels [36]. They are also relatively expensive but can often cut down costs by reducing operating time and embolization material required especially in larger vessels [37,39].

Covered stents. Covered stents consist of a metal mesh tube lined with synthetic membrane designed to prevent stent ingrowth and restenosis [40]. Braided mesh bodies are made of stainless steel or titan-nickel alloy (Nitinol) [36]. The stent covers of most vascular stents are made of polyethyleneterephthalate (PTE, Dacron) or polytetrafluoroethylene (PTFE), both biocompatible, thromboresistant materials that do not degrade over time [40]. Stents are either balloon-expandable or self-expandable [36].

Stents are not embolic agents per se but are useful especially when sacrificing the patency of the target artery is not an option. They can
effectively control hemorrhage by bridging the bleeding site. Vessel defect occlusion is immediate and does not depend on the coagulation status [36]. Covered stents also allow the endovascular management of visceral artery aneurysms and pseudoaneurysms that can be excluded from circulation by placing a covered stent across the aneurysm neck [17].

Stents may be difficult to position in tortuous arteries, which limits their use e.g. in the treatment of distal splenic artery aneurysms [17]. Stent thrombosis is a feared complication, although the well-developed collateral network of visceral arteries may sometimes prevent organ ischemia in acute thrombosis [41]. Thrombosis prophylaxis preferably with the dual antiplatelet therapy combining aspirin and clopidogrel should be considered at least for the first three months after visceral stenting.

**Flow-diverting stents.** Flow-diverting stents are new endovascular devices made of tubular mesh with different levels of porosity that allows altered aneurysmal blood flow and neointimal overgrowth [36,41]. They are designed to slow down the turbulent flow in the aneurysmal sac up to a point of stagnation and thrombosis. Eventually the neointimal overgrowth excludes the aneurysm from circulation and restores the laminar blood flow.

Flow-diverting stents are not suitable for acute bleeding situations because their design does not allow instant closure of the vascular area [36]. Flow diverters are primarily used to treat complex intracranial aneurysms [36]. They have also been used in the management of peripheral and visceral artery aneurysms with satisfactory results in technical success, aneurysm thrombosis, and patency of branch arteries, and with a stent thrombosis rate of 8.3% [41].

**Particles**

**Polyvinyl alcohol particles.** Polyvinyl Alcohol (PVA) is a synthetic nonabsorbable material indicated for permanent vessel occlusion. It was introduced in intravascular embolization in 1974 [37]. Today PVA is used in the form of PVA particles that obstruct the vessel by mechanical occlusion and by causing vascular inflammatory reaction and vessel fibrosis over time [36]. The traditional method of particle preparation by rasping dried PVA sheets into particles causes irregularity in particle size and shape. Due to the irregular shape the particles tend to aggregate, which may lead to catheter jamming and non-target embolization when a particle aggregate clogs the catheter hub and the catheter is being flushed [37]. Newer calibrated spherical particles are regular in shape and allow particle use with less aggregation-related problems. They are available in sizes ranging from 45 to 1200 µm [36].

PVA particles are useful predominantly in tumor and small vessel embolizations [34,38]. They are cheap, easy to use, and clog the smallest vessel where they fit. Particle embolization is flow-directed, which allows
upstream embolization without navigating the catheter all the way to the target artery. PVA particles are radiolucent. Aggregation-related problems are another downside [36]

**Acrylic microspheres.** Trisacryl gelatin microspheres (TAGMs) have indications similar to those of PVA particles. TAGMs are precisely calibrated acrylic spheres cross-linked with gelatin [36]. Their surface structure prevents them from aggregating, which causes less catheter occlusion and allows the TAGMs penetrate deeper into the vascular system than PVA particles of similar size [42]. TAGMs are available in sizes ranging from 40 to 1200 μm. In general, the chosen size should be larger than that of the PVA particles used in a corresponding situation [38]. Intermittent stirring keeps TAGMs in suspension until injected. TAGMs are compressible, allowing their easy passage through the catheter. Adding contrast material is necessary because the spheres are radiolucent. They may also have allergic potential due to porcine gelatin content.

**Liquid Embolic Agents**

**N-butyl-cyanoacrylate.** N-butyl-cyanoacrylate (NBCA) is an adhesive liquid embolic agent providing permanent vessel occlusion [36,37]. Mixing it with ethiodized oil (Lipiodol®) or tantalum powder makes the glue radiopaque. NBCA solidifies and causes vessel occlusion when coming into contact with ionic fluids such as blood or saline. It stimulates inflammatory reaction that eventually causes vessel fibrosis. Hence, the hemostatic effect does not depend on the patient’s coagulation status.

NBCA has been in the market since 2000 when FDA approved its intravascular use for cerebral arteriovenous malformations [43]. It is also used in peripheral embolizations including pseudoaneurysms, hepatic tumors, and hemorrhages requiring fast occlusion [36]. In upper and lower gastrointestinal bleeding NBCA seems to secure a good hemostatic result without any increase in ischemic complications when compared to other commonly used embolic agents [43].

NBCA is a cheap and fast-acting embolizing agent. However, high adhesiveness does not come without inconveniences, and the use of NBCA requires experience [36]. In the beginning, catheter needs flushing with a nonionic dextrose-water solution to prevent premature polymerization during injection. After a couple of glue injections the catheter tends to occlude. Solidified material can rip off and migrate when retracting the catheter without simultaneous aspiration. Improperly removed catheter tip can also get stuck in the glue within the vessel requiring the breaking of the catheter.

**Ethylene vinyl alcohol copolymer.** Ethylene vinyl alcohol copolymer (Onyx®) started gaining popularity as an embolic agent in interventional
neuroradiology some 10 years ago [44]. Today its indications cover also peripheral embolizations for small-vessel and medium-vessel hemorrhages, and the results e.g. in the treatment of lower gastrointestinal bleeding are good [45]. Onyx is a non-adhesive liquid embolic agent that consists of three primary elements: The polymer of ethylene and vinyl alcohol (EVOH) is a plastic polymer responsible for the occlusion. Dimethyl sulfoxide (DMSO) is a potent organic solvent containing the dissolved EVOH. Tantalum powder makes Onyx highly radiopaque [36]. The concentration of EVOH in DMSO solution defines the viscosity of Onyx that is commercially available in different viscosities.

Embolization with EVOH is independent of inherent coagulation. Onyx produces permanent vessel occlusion through precipitation that starts when it comes into contact with blood [36]. It solidifies from outside to inside, eventually forming a cast within the vessel lumen. Unlike cyanoacrylates, Onyx is not adhesive. Hence, it does not occlude the catheter canal or cause the catheter tip to get stuck in it. Embolization procedure is extremely safe due to perfect control of the agent; Onyx does not spread with blood flow but is displaced by pushing the cast or by pressure applied through the syringe by the operator [44]. It also has an excellent visibility in fluoroscopy.

Onyx needs stirring for at least 20 minutes before use. To avoid polymerization in the catheter during injection, the dead space of the catheter requires filling with DMSO [44]. DMSO may cause endothelial damage leading to vasospasm or even necrosis [36,37]. Due to its toxicity, it has to be injected slowly. The injection is painful without general anesthesia, although mesenteric embolizations may be better tolerated than the peripheral ones [46,47]. Another disadvantage of Onyx is its high price [46].

**Alcohol.** Alcohol is a well-known sclerosant that is widely available and inexpensive. It causes permanent vascular occlusion by inciting endothelial damage and perivascular necrosis through protein denaturation [36,37]. It is useful in embolization only when non-target embolization is unlikely, which is uncommon in the gastrointestinal tract. The disadvantages of absolute ethanol embolization include the radiopaucity of the agent, difficulty to control the placement, and rapid intravascular dilution with blood flow [48].

**Sclerosants.** Sclerosing agents like ethanolamine oleate, sodium tetradecyl sulphate, polidocanol and sodium morrhuate result in vessel occlusion through vascular injury and fibrosis [16]. Non-target embolization is a concern in their intra-arterial use, and sclerosants are mainly used in venous disease such as superficial varicose veins and varicocele [48]. Due to extravasation, sclerosants may cause soft tissue necrosis [48].
**Reabsorbable Materials**

*Gelatin.* Gelatin was first used in arterial embolization in 1964 [49]. It is a pork skin-derived water-soluble hemostatic material that is commercially available in sterile sheets, particles and powder. Gelatin produces temporary hemostasis that typically lasts from 3 to 6 weeks [38]. The hemostatic effect is a result of its ability to absorb liquid 45 times its weight, drying the tissue and causing platelet entrapment [36].

Gelatin is an inexpensive embolization agent that is most often used e.g. in traumatic and post-partum hemorrhages, and tumor embolizations before surgery [36]. It is not a good alternative in coagulopathic patients. Gelatin sponge is associated with a small risk of infections, which may be related to air retention in its spongy structure and contamination with air-borne bacteria.

*Thrombin.* Thrombin is a natural enzyme promoting clot formation by converting fibrinogen into fibrin [34]. Its most prevalent use is in treating iatrogenic pseudoaneurysms complicating arterial puncture and catheterization.

### 2.1.5 ADVERSE EFFECTS AND SAFETY

**Contraindications**

As arterial embolization is often a life-saving procedure, absolute contraindications do not exist. Relative contraindications include uncontrollable coagulopathy, renal insufficiency and contrast allergy [16]. The history of life-threatening contrast reaction is a serious contraindication where CO₂-enhanced angiography is a potential alternative. In massive bleeding, surgery may provide a quicker hemostasis.

**Peri- and Post-Operative Complications**

Complications related to arterial puncture and catheterization are inherent to all angiograms. They include hematomas, pseudoaneurysms, hemorrhages, and arterial dissection and occlusion [16]. Hematomas rarely require more than observation. Puncture site pseudoaneurysms can usually be managed with ultrasound guided thrombin injections. Retroperitoneal hematoma with ongoing bleeding can be life-threatening and requires surgical repair. Arterial dissection especially in larger arteries may warrant endovascular stenting [16].

Non-target embolization is a feared technical complication that may lead to end-organ ischemia. It may occur as a result of distal migration of embolic material e.g. due to inappropriate vessel sizing or device selection [27,50].
Another possible mechanism is the reflux of particles during injection especially in high-resistance environment [51]. Catheter tip may also bounce back from the arterial ostium during coil deployment, leading to a more proximal embolization than intended [37]. In these cases misplaced coils are often retrievable whereas misplaced particles and glue are not [52]. Delayed coil migration may also occur: Case reports describe e.g. gastric ulceration due to coil penetration and the passing of coils per rectum [53-55]. Migrating coil material can also compress or erode the biliary ducts causing obstructive jaundice and cholangitis [56,57].

Embolization complicated by end-organ ischemia may result in splenic or hepatic infarction, necrosis and abscess [16,50] (Figure 2). It may also lead to the infarction and perforation of the gastrointestinal tract. Post-embolization syndrome after hepatic artery embolization refers to the combination of abdominal pain, nausea, fever and elevated liver enzymes. It can also occur after splenic artery embolization and present itself with upper abdominal pain, fever and elevated levels of serum inflammatory markers [58]. Finally, the introduction of exogenous bacteria through arterial puncture may lead to bacteremia and sepsis [50]. Antibiotic prophylaxis may decrease infectious complications in procedures where bacterial contamination is likely (e.g. in colon and some hepatic embolizations) [59].

**Contrast-Related Adverse Effects**

**Contrast-induced nephropathy.** Contrast-induced nephropathy (CIN) refers to the acute deterioration of renal function occurring 48–72 hours after intravenous contrast administration [60]. It accounts for 10% of hospital acquired renal insufficiency, ranking third after dehydration and nephrotoxic medication [61]. The risk of CIN is extremely low when glomerular filtration rate (GFR) is over 60 ml/min. Patients with the GFR less than 30 ml/min are at the highest risk. Other risk factors include diabetes, multiple
comorbidities, advanced age, nephrotoxic medication, hypotension and acute illness [60]. When compared to intravenous contrast use, the risk of CIN is significantly higher after intra-arterial contrast administration [60]. Hence, preventive measures are recommendable in intra-arterial contrast use for patients with the GFR less than 60 ml/min.

Initial observations on CIN derive from early studies with high-osmolar iodinated contrast media [62]. However, contemporary imaging utilizes mainly low- and iso-osmolar ICM, the nephrotoxic effects of which are currently widely questioned [62,63]. A recent large retrospective cohort study suggests that ICM are not associated with the increased risk of CIN in current clinical context [64]. Randomized controlled trials do not exist, and guidelines continue to recommend preventive strategies such as intravenous hydration and the discontinuation of nephrotoxic medication before contrast administration especially in high risk groups [60]. The rule is to consider alternative imaging methods and contrast agents whenever possible and to use only the minimum amount of contrast that allows good image quality [61].

**Hypersensitivity reactions.** The estimated incidence of allergic reactions to ICM is 1:170 000, with hypersensitivity reactions occurring in 0.05-0.1% of patients [65]. Symptoms are usually mild to moderate. Life-threatening reactions are rare – mortality ranges from 1-3 per 100 000 administrations.

The pathophysiological mechanisms of ICM-induced hypersensitivity reactions are not clear [65]. The symptoms were traditionally considered anaphylactoid rather than allergic, but the growing body of evidence suggests that underlying immunological mechanisms exist in at least some of the reactions.

**Immediate reactions** occur within an hour of contrast administration and present as erythema and urticaria with or without angioedema in 70% of patients [65]. More severe symptoms include dyspnea, nausea and vomiting, hypotension, and anaphylactic shock. **Non-immediate reactions** emerge more than an hour up to three days after the administration of ICM. They consist of maculopapular rash or delayed urticaria and usually resolve spontaneously within a week. **Non-allergic reactions** such as facial flushing, dizziness and nausea are self-limiting and appear immediately after the ICM administration.

Sufficient follow-up is important after contrast-enhanced imaging [65]. If hypersensitivity symptoms develop, the immediate discontinuation of ICM administration is necessary. Corticosteroids, antihistamines, inhaled β₂-agonists, or epinephrine injections may prove helpful. All ICM-induced reactions warrant subsequent allergy workup and, thus, require proper documentation. Non-allergic reactions do not necessitate further examinations.
Exposure to Ionizing Radiation

Out of all therapeutic procedures in non-cardiac interventional radiology, patients have the highest radiation doses in visceral embolization procedures [66,67]. Prolonged fluoroscopy time with the acquisition of multiple images is often necessary, increasing the radiation exposure of patients and medical staff. In complicated procedures, patients sometimes receive skin doses of over 2 Gy [66,67]. This is a threshold for acute skin reactions like erythema and epilation. The stochastic effects of radiation are always a concern, also with lower doses. The International Commission on Radiological Protection (ICRP) recommends patient counseling before high-risk procedures [68]. Skin doses above 3 Gy should be recorded. After higher doses, patients should be followed up for 10-14 days to detect potential radiation injuries. However, measuring patient doses is not always routine clinical practice, making the ICRP recommendation difficult to follow [67].

2.2 ARTERIAL EMBOLIZATION IN GASTROINTESTINAL BLEEDING

2.2.1 BACKGROUND

Percutaneous selective angiography was first described as a safe and effective method for the pre-operative diagnosis of gastrointestinal bleeding in 1963 [32]. The first embolization procedure took place in 1971 in the United States, where Charles Dotter’s group used autologous blood clot in embolizing the right gastroepiploic artery to control UGIB [27]. In the 1970’s and 1980’s TAE was experimented also in LGIB, but the attempts were often complicated with post-embolization ischemia [32]. The development of microcatheters and the simultaneous evolution of embolic coils in the late 1980’s enabled superselective mesenteric embolizations in vasa recta level. This minimized the risk of ischemia and made TAE a standard method also in LGIB [32].

2.2.2 UPPER GASTROINTESTINAL BLEEDING

Upper gastrointestinal bleeding warrants arterial embolization when endoscopic treatment fails or is not feasible or when bleeding recurs after endoscopic hemostasis [16]. The typical patient presents with hemodynamic instability or continuous bleeding that has not responded to medical management and at least one attempt of endoscopic hemostasis [69].
### Table 1

The 30-day outcomes of recent case-control studies comparing transcatheter arterial embolization (TAE) and surgical treatment (ST) in upper gastrointestinal bleeding of various etiologies

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>TAE</th>
<th>ST c</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laursen et al. (2014) [71]</strong> 1997-2013 n = 24 n = 73</td>
<td>91.7</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%) a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%) b</td>
<td>25</td>
<td>15</td>
<td>0.02</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>37.5</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>12.5</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td><strong>Ang et al. (2012) [72]</strong> 2004-2010 n = 45 n = 63</td>
<td>89</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>40</td>
<td>12.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>38</td>
<td>60.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>29</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Wong et al. (2011) [8]</strong> 2000-2009 n = 30 n = 56</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>46.7</td>
<td>12.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>46.7</td>
<td>67.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>16.7</td>
<td>30.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Venclauskas et al. (2010) [73]</strong> 2000-2007 n = 32 n = 50</td>
<td>88.5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>34.4</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>40.6</td>
<td>66.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>25</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Langner et al. (2008) [74]</strong> 2000-2006 n = 24 n = 12</td>
<td>NR</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>15</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>54.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>20.8</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Eriksson et al. (2008) [9]</strong> 1998-2005 n = 11 n = 51</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>27</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>NR</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>27</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Defreyne et al. (2008) [75]</strong> 1993-2003 n = 40 n = 51</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Technical success (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent bleeding (%)</td>
<td>25</td>
<td>25.4</td>
<td>NR</td>
</tr>
<tr>
<td>Complication rate (%)</td>
<td>20</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>3</td>
<td>27.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

NR: Not reported, NS: Non-significant (P ≥ 0.05), TAE: Transcatheter arterial embolization

a: Technically feasible procedure with post-embolization angiogram showing the discontinuation of bleeding

b: Recurrence of bleeding symptoms within 30 days of TAE

c: Multiple techniques described (ulcer underrunning in duodenotomy/gastrotomy, gastric ulcer excision, subtotal and total gastrectomy with or without truncal vagotomy)
Embolization procedure for UGIB begins by localizing the bleeding with angiogram \([16,69]\) (Figure 3). The most likely sources are the gastroduodenal artery (GDA) and the left gastric artery (LGA) that require selective catheterization. Coils, NBCA and gelatin sponge are all applicable embolic agents. A common embolization method is the sandwich technique permitting the control of the back and front doors of the bleeding site in the area of rich collateral vasculature. After the embolization of the GDA, the angiogram of the SMA is necessary to identify potential collateral flow from the pancreaticoduodenal arcade. When the initial angiogram remains negative in the setting of ongoing bleeding, the empirical embolization of the GDA in duodenal pathology or the LGA in proximal gastric pathology is an option. To facilitate this, the endoscopist can mark the bleeding site with metallic clips that are visible in fluoroscopy \([70]\).

The technical success of arterial embolization in UGIB is usually over 90% but varies from 52 to 100% \([8,9,71-78]\). Recent case series report recurrent bleeding in 0-36% of patients \([69,79]\). Predictors of recurrent bleeding include comorbidities, coagulopathy, hemodynamic instability, active bleeding in endoscopy, large ulcer size, ulcer location in posterior duodenum or lesser gastric curvature, and the use of coils as the only embolic material \([78,80]\). Some advocate prophylactic embolization after successful endoscopic hemostasis in these high-risk patients \([81,82]\). Embolization complication rates in UGIB vary from 0 to 16% \([69,77]\). Due to rich collateral vasculature above the ligament of Treitz, end-organ ischemia is rare. In addition to angiography-related complications, potential complications include duodenal stenosis, ischemic pancreatitis, and the non-target embolization of hepatic artery with various possible consequences \([69,77]\). Coil migration causing gastric ulceration may also occur \([83-85]\).

Current guidelines on the management of UGIB rely on single-center case series and retrospective case-control studies \([7-9,71-75,79,86]\) (Table 1). After failing endoscopy, the guidelines recommend TAE or surgery as the second-line approach, but consensus on the preferable method remains
unestablished [2,87,88]. Randomized controlled trials comparing TAE and surgery do not exist. Meta-analyses combining data from retrospective case-control studies suggest a higher rebleeding rate after TAE but no significant difference in mortality between the two methods [77,89]. The findings from a recent population-based cohort study from Sweden are consistent with the higher likelihood of recurrent bleeding after embolization, but they also show higher morbidity and mortality after surgery [90]. The advantageous safety profile of TAE often justifies the risk of recurrent bleeding, and many favor TAE over surgery when endoscopic treatment fails.

2.2.3 LOWER GASTROINTESTINAL BLEEDING

When colonoscopy fails or is not feasible, the indications of TAE in LGIB include ongoing bleeding documented in CTA and massive bleeding with hemodynamic compromise [16]. The typical candidate presents with blood and blood clots per rectum with hemodynamic instability or constant requirement for blood transfusions [91].

Before angiography, cross-sectional imaging with CTA enables localizing the bleeding [92]. If extravasation is visible in the small intestine, right hemicolon or transverse colon, catheterizing the SMA initiates the angiography [32]. The IMA is selected first when bleeding originates in the left hemicolon or sigmoid. In rectal bleeding the internal iliac artery may be the feeding artery. Catheterizing the coeliac axis allows detecting anatomic variants or a bleeding duodenal ulcer when the mesenteric and internal iliac angiographies remain negative.

The diagnostic yield of mesenteric angiography is 40-86% [93]. A preceding positive CTA has the potential to double the yield, whereas a long delay between the CTA and the mesenteric angiography often decreases the yield [94]. To increase the diagnostic yield, some advocate administering provocative medication such as vasodilators, thrombolytics or anticoagulants during angiography [95]. Provocative angiography may enable diagnosing the extravasation in up to 30% of patients with initially negative angiographies [95].

Mesenteric embolization can be technically demanding due to vessel tortuosity, vasospasm and atherosclerotic plaques [32]. The procedure requires microcatheters and super-selective catheterization of vasa recta arteries. A more proximal embolization in the level of marginal arteries may result in bowel ischemia (Figure 4). Microcoils are the most common embolic agent. Small PVA particles migrate distally with blood flow and have the potential to occlude the collateral vasculature of the bowel wall causing ischemic complications.

The technical success rates of TAE in LGIB range from 90 to 100% [96-106] (Table 2). Recurrent bleeding occurs in 9-26% of patients and can be
Table 2  Summary of recent studies reporting the safety and efficacy of transcatheter arterial embolization in lower gastrointestinal bleeding

<table>
<thead>
<tr>
<th>Author</th>
<th>Recruitment</th>
<th>Patients (n)</th>
<th>Technical success (%)</th>
<th>Recurrent bleeding (%)</th>
<th>Ischemia (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senadeera et al. 2018</td>
<td>2007-2017</td>
<td>77</td>
<td>97</td>
<td>19</td>
<td>5.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Bua-ngam et al. 2017</td>
<td>2007-2015</td>
<td>39</td>
<td>92</td>
<td>26</td>
<td>13</td>
<td>31.5^{f}</td>
</tr>
<tr>
<td>Hur et al. 2014</td>
<td>2006-2013</td>
<td>112</td>
<td>96.4</td>
<td>17.4</td>
<td>4.6</td>
<td>25^{f}</td>
</tr>
<tr>
<td>Teng et al. 2013</td>
<td>1997-2009</td>
<td>26</td>
<td>84.6</td>
<td>17.7</td>
<td>7.7^{e}</td>
<td>19.2</td>
</tr>
<tr>
<td>Huang et al. 2011</td>
<td>2006-2008</td>
<td>27</td>
<td>100</td>
<td>14.8</td>
<td>0</td>
<td>4.4</td>
</tr>
<tr>
<td>Gillespie et al. 2010</td>
<td>1998-2008</td>
<td>38</td>
<td>93</td>
<td>24</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td>Maleux et al. 2009</td>
<td>1997-2008</td>
<td>39</td>
<td>100</td>
<td>15</td>
<td>10^{e}</td>
<td>15</td>
</tr>
<tr>
<td>Frodsham et al. 2009</td>
<td>2005-2009</td>
<td>14</td>
<td>100</td>
<td>14</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Koh et al. 2009</td>
<td>2000-2006</td>
<td>68</td>
<td>100</td>
<td>8.8</td>
<td>5.9</td>
<td>0</td>
</tr>
<tr>
<td>Tan et al. 2008</td>
<td>2000-2007</td>
<td>32</td>
<td>97</td>
<td>22</td>
<td>3^{e}</td>
<td>9</td>
</tr>
<tr>
<td>Lipof et al. 2008</td>
<td>1999-2005</td>
<td>75</td>
<td>97</td>
<td>16</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>

^{a} Technically feasible procedure with post-embolization angiogram showing the discontinuation of bleeding

^{b} Recurrence of bleeding symptoms within 30 days of embolization

^{c} Ischemic complications within 30 days of embolization

^{d} Death within 30 days of embolization

^{e} Ischemic complications requiring bowel resection

^{f} In-hospital mortality
self-limiting or require surgical intervention or repeated embolization. The rate of major complications varies from 0 to 25% [98]. Ischemic complications are the most common and vary from transient abdominal pain and spontaneously resolving ischemic ulcers to surgery-requiring bowel perforation and peritonitis [32]. Reported mortality rates usually range from 2 to 30%, but some studies show exceptionally high rates up to 56% [98]. Nevertheless, arterial embolization is the recommended approach over surgery in LGIB, surgery being reserved only for situations where other modalities fail or are not feasible [93].

**Figure 4**  Transcatheter arterial embolization (TAE) of diverticular bleeding in sigmoid colon. Contrast extravasation in sigmoid colon in computerized tomography scan (1A-B). Extravasation in inferior mesenteric artery angiogram (2A). Embolization coils in vasa recta arteries and marginal arteries in post-embolization angiogram (2B). Sigmoid diverticula and transmural bowel wall ischemia in sigmoidoscopy two days after TAE (3A-B). Adapted from Nykänen et al. (2018) with the permission of the original copyright holder (Transcatheter arterial embolization in lower gastrointestinal bleeding – ischemia remains a concern even with a super-selective approach. J Gastrointest Surg 2018;22:1394:1403) [30].
2.2.4 VISCERAL ARTERY ANEURYSMS AND PSEUDOANEURYSMS

Endovascular management with embolization or stenting is the preferred treatment approach of visceral artery aneurysms and pseudoaneurysms in both, elective and emergency situations. Watchful waiting is usually sufficient in non-symptomatic true aneurysms. Visceral pseudoaneurysms require interventional management regardless of their size and etiology. Table 3 summarizes the indications for intravascular interventions [16,17].

Visualizing the vascular anatomy allows for the careful planning of intravascular procedures, and CTA or MRA should always precede TAE [16]. TAE procedure begins by gaining arterial access and selectively catheterizing the parent artery. Embolization strategy depends on whether sacrificing the patency of the parent artery is safe. Depending on the anatomy, various embolic agents and embolization techniques are applicable (Figure 5).

The aneurysm can be isolated by occluding the aneurysmal artery first distal and then proximal to the aneurysm neck [16,17]. In this so-called sandwich technique, coils and AVPs are both useful embolic agents. Another method in saccular aneurysms with narrow necks is the coil packing of the aneurysm. This causes the thrombosis of the aneurysm but leaves the parent artery intact. True aneurysms with wide necks sometimes require coil packing through a bare stent. Covered stents and flow-diverting stents are also used to isolate visceral artery aneurysms and pseudoaneurysms, although flow diverters are not suitable for the emergency interventions of ruptured aneurysms due to their design [36,41]. Liquid embolic agents like Onyx® and NBCA may be useful in aneurysms of tortuous arteries where the pushability of coils is limited [16,17]. They are also useful in filling the aneurysm sack when the parent artery has to remain patent. Thrombin injection directly into the aneurysm sack is a useful method especially in pseudoaneurysms.

Table 3

<table>
<thead>
<tr>
<th>Aneurysms</th>
<th>All symptomatic (pain, hemorrhage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Increase in size (over 0.5 cm over a year)</td>
</tr>
<tr>
<td></td>
<td>Size of over 2-2.5 cm in splenic, hepatic and coeliac arteries</td>
</tr>
<tr>
<td></td>
<td>Non-pregnant women of child-bearing age</td>
</tr>
<tr>
<td></td>
<td>Patients that may require liver transplant</td>
</tr>
<tr>
<td></td>
<td>All sizes in rare locations (IMA, SMA, and their branches)</td>
</tr>
<tr>
<td></td>
<td>Non-atherosclerotic etiology</td>
</tr>
<tr>
<td>Pseudoaneurysms</td>
<td>All regardless of size and etiology</td>
</tr>
</tbody>
</table>

IMA Inferior mesenteric artery; SMA Superior mesenteric artery
Figure 5  Endovascular treatment approaches for visceral artery aneurysms and pseudoaneurysms. Stent exclusion of a proximal splenic artery pseudoaneurysm with active contrast extravasation. Patent arterial blood flow with spasm visible in the splenic artery in post-stenting angiogram (1A-B). Stent exclusion of a common hepatic artery aneurysm (2A-B). Coil-embolization with sandwich technique in a splenic artery pseudoaneurysm (3A-B). Coil-packing of hepatic artery aneurysms (4A-B).
When embolizing splenic artery aneurysms especially close to splenic hilum, partial splenic infarction may occur. Ischemic complications are less prevalent in proximal embolizations where collateral vasculature from short gastric arteries remains patent. Although various studies confirm the preservation of splenic immune function after splenic artery embolization, providing patients with post-splenectomy immunizations after TAE remains controversial [16,107].

The dual blood supply of the liver allows the embolization of hepatic artery branches with a minimal risk of ischemia when the portal vein is patent. Nevertheless, hepatic artery embolizations carry a risk of post-embolization syndrome, hepatic necroses, hepatic abscesses and cholecystitis [16,17]. In aneurysms occurring in the GDA and its branches, arterial occlusion is safe when the coeliac axis and the SMA are patent.

The technical success rates of embolizations for visceral artery aneurysms and pseudoaneurysms are 89-98% [17]. The mortality after elective procedures is very low – three recent case series report a 30-day mortality of 0% [18,108,109]. The figures are notably different for ruptured aneurysms and pseudoaneurysms, where Pitton et al. show 30-day rebleeding and mortality rates of 16.7% and 6.7%, respectively [18]. Pancreatic pseudoaneurysms are a specific subgroup of visceral artery pathology. In their endovascular management the clinical success rates range from 67-97% and mortality rates from 4-19% [21,22,110,111].

2.2.5 HEMORRHAGIC TUMORS

Ruptured Hepatic Tumors

Arterial embolization is the first-line hemostatic intervention in hemodynamically unstable patients with the spontaneous rupture of benign and malignant hepatic tumors [23,112,113]. Definitive surgical resection may be planned as a staged procedure after the confirmation of etiology and tumor stage, and the assessment of hepatic function.

Diagnostics with CT or preferably CTA should precede all hepatic tumor embolizations. Intrahepatic hematoma or intraperitoneal hemorrhage from a ruptured subcapsular tumor, with or without active extravasation, confirms the diagnosis [24]. CTA allows the exact localization of bleeding, the detection of vascular anatomical variants, and the estimation of portal vein patency. Although only up to 50% of hepatic artery angiograms show active extravasation, tumor staining is usually detectable and allows the localization of bleeding together with CTA findings (Figure 6) [25,114]. Hepatic artery embolization is preferably carried out in the level of segmental arteries feeding the tumor. Lobar embolization by occluding the right or left hepatic artery is sometimes necessary but carries a higher risk for hepatic failure.
Coils and particles are the common embolic agents. Some advocate using gelatin sponge rather than permanent embolic material especially in HCC to later facilitate chemoembolization [24].

In the treatment of bleeding hepatic tumors, TAE is feasible in more than 90% of patients and controls the bleeding in over 80% [23]. The most common complication in 26-85% of patients is post-embolization syndrome consisting of fever, abdominal pain, nausea, and elevated liver enzymes [113]. Hepatic ischemia leading to necroses and abscesses may also occur. The risk of hepatic failure is considerable especially in patients with poor hepatic function or portal vein thrombosis. The 30-day mortality depends on the underlying tumor etiology and varies from 0-38% [113-115]. Results are good in patients with malignant tumors that are amenable to further surgical management and in patients with benign tumors. Mortality is high among cirrhotic HCC patients with poor hepatic function [116]. Absolute contraindications do not exist, but contrast allergy and complete portal vein thrombosis are considered relative contraindications. Embolization is unlikely to benefit patients that have end-stage cirrhosis and the bilirubin level of over 50 µmol/l [113]. It is also debated whether TAE offers survival
benefit in hemodynamically stable patients by reducing their risk of recurrent bleeding and causing regression in tumor size [113,117].

**Tumors Invading the Gastrointestinal Tract**

Arterial embolization may allow a bridge for definitive surgery and preceding neoadjuvant therapy e.g. in patients with gastric and rectal tumors presenting with acute bleeding. After failing endoscopy, it is the second-line treatment in inoperable advanced tumors invading the gastrointestinal tract and causing acute or chronic bleeding [118]. In a study by Tandberg et al. (2012) on 23 patients with various advanced abdominal malignancies, TAE was successful in controlling the bleeding in 68% of patients [119]. No ischemic complications or major mortality occurred within 30 days of TAE. The majority of tumors were identifiable in angiography even in the absence of active extravasation. The authors concluded that arterial embolization is a useful palliative therapy in these patients that otherwise have very few treatment options. Indeed, embolization is often effective in controlling the acute bleeding. However, recurrent bleeding especially in inoperable tumors is devastatingly common, with 30-day rebleeding rates e.g. in unresectable gastric cancer reaching 48-60% [120,121].

### 2.3 ALTERNATIVE HEMOSTATIC METHODS

#### 2.3.1 ENDOSCOPIC HEMOSTASIS

**Upper Gastrointestinal Bleeding**

The first-line intervention in the diagnostics and management of upper gastrointestinal bleeding is upper endoscopy [87,88]. It allows visualizing the bleeding site with simultaneous hemostatic interventions such as fibrin glue injection, through-the-scope clipping or thermal coagulation. Novel methods like hemostatic powder (Hemospray®) and over-the-scope clipping have also been used. Being associated with less blood transfusions, shorter hospital stays and lower mortality, guidelines recommend early endoscopy within 24 hours of hospitalization [87]. Additional hemostatic procedures due to failing endoscopic treatment or recurrent bleeding after endoscopic therapy are necessary in less than 4% of patients [6].

**Lower Gastrointestinal Bleeding**

The first-line method in the diagnostics and management of LGIB is colonoscopy (Figure 7). The reported diagnostic yield of colonoscopy is 74-
100% [122]. Some 10-40% of patients receiving urgent colonoscopy for LGIB undergo hemostatic intervention. The most common hemostatic method is thermal coagulation after adrenalin injection. Hemoclips, argon coagulation and rubber bands have also been used. Complications are rare and occur in only 0.6% of urgent colonoscopies [122].

**Figure 7** Treatment of profuse lower gastrointestinal bleeding in a patient with coronary heart disease and concomitant myocardial infarction. Endoscopic clipping attempt in diverticular bleeding (1A-B). Recurrent bleeding and active contrast extravasation in computerized tomography angiography scan (2A-B). Negative angiogram showing endoscopic metallic clips but no contrast extravasation (3A). Empirical embolization attempt with coils in vasa recta and marginal arteries adjacent to endoscopic clips (3B). Post-embolization ischemia with perforation and peritonitis necessitated laparotomy and bowel resection two days after embolization. Adapted from Siironen and Nykänen (2018) with the permission of the original copyright holder (Acute lower gastrointestinal bleeding, Duodecim 2018;134:1156–64) [91].
Guidelines recommend early colonoscopy within 24 hours of hospitalization especially in patients with signs of active bleeding [92,123]. Early colonoscopy increases the diagnostic yield and the likelihood of therapeutic intervention and is associated with shorter hospital stays. Rapid colon preparation is important before the examination to increase visualization. Poor bowel prep, abundant bleeding and the lack of experienced endoscopy team outside regular working hours may limit the diagnostic potential of emergency colonoscopy. Massive bleeding with hemodynamic instability is a contraindication to colonoscopy and warrants urgent CTA and referral to embolotherapy.

2.3.2 SURGICAL HEMOSTASIS

**Upper Gastrointestinal Bleeding**

Surgery is a rational hemostatic approach after endoscopy especially in patients that have deforming or penetrating ulcers causing simultaneous pyloric stenosis or perforation. Depending on the underlying etiology of UGIB, various surgical methods can be employed. The most straightforward approach is the oversewing of the bleeding ulcer in gastrotomy or duodenotomy [124]. Large or deforming ulcers may require resections such as gastric wedge resection, distal gastrectomy, or even total gastrectomy in extensive proximal gastric pathology [124,125]. Truncal vagotomy was traditionally performed as an additional procedure in peptic ulcer surgery to suppress acid production. Protein pump inhibitors have replaced vagotomy, and it is not a routine procedure in modern practice [125].

Several retrospective case-control studies have compared the safety and efficacy of TAE and surgery in the treatment of UGIB (Table 1). After surgical treatment, these studies show a 30-day recurrent bleeding rate of 8-25%, complication rate of 30-68%, and mortality rate of 14-30% [7-9,71-75,86]. A Swedish nationwide population based cohort study did not reveal any difference in 30-day, 90-day, 1-year and 5-year survivals in patients managed with minimal surgery (oversewing the ulcer with or without arterial ligation, or local excision of the ulcer) or definitive surgery (resection of a part of the duodenum or stomach with or without vagotomy) for bleeding gastric and duodenal ulcers [124].

**Lower Gastrointestinal Bleeding**

The surgical treatment of LGIB is often a challenge due to difficulties in localizing the bleeding. Surgery is the last resort when endoscopic and intravascular approaches fail or are not feasible in patients with unstable hemodynamics or recurrent bleeding [126]. Applicable interventions include
the segmental small bowel resection, subtotal colectomy, and the segmental resection of colon [127]. Blind segmental colectomies are associated with rebleeding rates of around 40% and mortality rates of up to 57% [127]. Thus, segmental resection should be carried out only when the bleeding site is identified. Otherwise, the alternative is blind subtotal colectomy with or without stoma. Every effort should be made to localize the bleeding before the surgical intervention. Intraoperative colonoscopy and enteroscopy are sometimes useful in localizing the bleeding during the operation [126]. The overall mortality from surgery for LGIB according to a recent review is 15.9-17% [126].

**Visceral Artery Aneurysms and Pseudoaneurysms**

The surgical treatment of visceral artery aneurysms includes several alternatives depending on the location and the size of the aneurysm. Aneurysm resection with primary end-to-end anastomosis is the most common method [109,128,129]. Other approaches include aneurysm ligation especially in bleeding aneurysms and aneurysm resection and arterial reconstruction with prosthesis in large aneurysms. Emergency repairs of ruptured aneurysms are associated with a higher morbidity and mortality than elective surgery. In a case-control study from Shukla et al. (2015) the major morbidity after surgery for non-ruptured and ruptured visceral artery aneurysms was 2.5% and 28.6%, respectively [128]. In a case series from Regus et al. (2016) including ruptured and intact true aneurysms, the 30-day mortality was higher after surgery than after endovascular treatment (20% vs. 0%, \( P = 0.038 \)) [109].

**Bleeding pancreatic pseudoaneurysms.** Emergency surgery for bleeding pancreatic pseudoaneurysms is associated with high morbidity and mortality. Nevertheless, it may be necessary when the patient presents with continuous bleeding and TAE fails or is not feasible [22]. The surgical approach depends on the location of the pathology. Management options include the excision of the pseudoaneurysm and pseudocyst, the ligation of the aneurysmal artery and drainage of the pseudocyst, and pancreatic tail resection in the pseudoaneurysms of pancreatic body and tail [130].

Studies on the surgical management of bleeding pancreatic pseudoaneurysms are scarce. A case-series by Kiviluoto et al. (1984) described 18 patients undergoing surgical treatment for bleeding pancreatic pseudocysts in chronic pancreatitis [131]. Out of 18, seven patients underwent partial or total pancreatectomy and 11 patients received transcystic suture ligation combined with the external drainage of the pseudocyst. Recurrent bleeding occurred in five patients (28%). In-hospital mortality was 33% (six patients). A case-series by Carr et al. (2000) described 13 surgically treated patients with the initial technical success of 69%, recurrent bleeding rate of 9%, complication rate of 62% and mortality
rate of 23% [132]. The authors observed a trend towards increased mortality after emergency surgery (50%). A more recent case series by Udd et al. (2007) included ten patients with failed arterial embolization [21]. Out of ten, six underwent distal pancreatectomy, three received suture ligation of the bleeding artery, and one was managed with pseudocystojejunostomy. The complication rate and mortality rate were 10%, respectively.

**Hemorrhagic Tumors**

**Bleeding hepatic tumors.** Before arterial embolization becoming standard treatment, laparotomy with hepatic packing or emergency hepatic resection was the method of choice in hepatic tumor hemorrhage. Emergency hepatic resections are associated with a high rate of morbidity and mortality, and today a resection is often performed as a staged procedure after first controlling the bleeding with TAE and stabilizing the patient [113].

The surgical results depend on the indication and extent of the procedure and the hepatic function. In HCC, one-stage hepatic resections have an in-hospital mortality of 16.5-100% [113]. Staged liver resections after optimizing the patient for general anesthesia and surgery have a lower in-hospital mortality of 0-9% [113]. Resections for hepatocellular adenoma carry a morbidity of 0-38% and a very low risk for mortality. A case-control study by Addeo et al. (2016) comparing the safety of liver resection in patients with hemorrhagic and non-hemorrhagic HCA found zero mortality and minimal morbidity in both groups with no difference between the groups [133]. The authors concluded that surgical resection offers definitive treatment and is safe even in an emergency setting in these usually young and otherwise healthy patients.

**Tumors invading the gastrointestinal tract.** As discussed earlier, recurrent bleeding is common after TAE and may warrant surgery in advanced tumors invading the gastrointestinal tract. Minimal surgical approach enabling the controlling of bleeding should be utilized in advanced stages. Localized tumors without distant metastasis may allow definitive surgical management according to the general oncologic principles.
3 AIMS OF THE STUDY

The doctoral thesis aimed at analyzing the safety, efficacy and feasibility of transcatheter arterial embolization in the treatment of non-traumatic gastrointestinal bleeding. The individual objectives of each study are listed below.

I:
To analyze the safety, efficacy and feasibility of the non-surgical management of bleeding pancreatic pseudoaneurysms by combining transcatheter arterial embolization and therapeutic endoscopy

II:
To compare the safety, efficacy and feasibility of transcatheter arterial embolization and surgical management in the treatment of bleeding gastric and duodenal ulcers

III:
To analyze the safety, efficacy and feasibility of transcatheter arterial embolization in the treatment of lower gastrointestinal bleeding

IV:
To analyze the safety, efficacy and feasibility of transcatheter arterial embolization in the treatment hepatic tumor hemorrhage
4 MATERIALS AND METHODS

4.1 RESEARCH SETTING

The study was carried out between 2014 and 2018 at the Abdominal Center of the Helsinki University Hospital. The Helsinki University Hospital is a secondary and tertiary referral hospital providing elective and emergency care for a population of 1.6 million people. Among other emergency services, the services of interventional radiologists including arterial embolization are available 24 hours a day. Patient referrals comprise referrals from primary health care providers in the area and other secondary referral hospitals without suitable interventional facilities.

4.2 STUDY DESIGN

Studies I, III and IV are retrospective studies. Study II is a retrospective case-control study.

4.3 PATIENTS

4.3.1 PATIENT IDENTIFICATION

Interventional codes for visceral artery angiographies and embolizations enabled identifying the study patients from the Picture Archiving and Communication System (PACS) of the Helsinki University Hospital. Each patient was allocated in one of the four study groups based on the bleeding site.

In Study I, ICD10 codes K85-K86 for acute and chronic pancreatitis and their complications enabled the identification of patients undergoing surgical treatment for bleeding pancreatic pseudoaneurysms from the hospital surgical interventions database.

In Study II, ICD10 codes for bleeding gastric and duodenal ulcers (K25.0, K25.4, K26.0, K26.4) and the Nordic Classification of Surgical Procedures codes for gastrotomy, duodenotomy and gastric resection (JDA00, JDH00, JDC00, JDC10) allowed the identification of surgically treated control group from the hospital surgical interventions database.
4.3.2 INCLUSION AND EXCLUSION CRITERIA

**Study I**

Study I screened 74 patients and included 58 patients treated for bleeding pancreatic pseudoaneurysms during 2004-2014. Inclusion criteria included 1) history with the episode of acute pancreatitis or underlying chronic pancreatitis complicated with a bleeding pancreatic pseudoaneurysm, and 2) the use of TAE as the first-line method to control the bleeding, followed by the staged endoscopic management of any remaining pseudocysts. The diagnosis of the bleeding pseudoaneurysm was based on CT scan findings. CT images, endoscopic retrograde cholangiopancreatography (ERCP) findings and laboratory results, including fecal elastase level, confirmed the diagnosis of the underlying pancreatitis. The study excluded patients treated for acute necrotizing pancreatitis complicated by in-hospital hemorrhage, patients with no underlying pancreatitis, and patients directly allocated to surgical management.

**Study II**

During 2000-2015, bleeding gastric and duodenal ulcers led to 1583 hospital admissions in the Helsinki University Hospital. TAE or surgery was necessary on 85 patients (5%). Out of 85, the study included 67 patients that received TAE or surgery for active or recurrent bleeding after failed endoscopic hemostasis. The study excluded 18 patients that underwent angiography with the primary intention to localize the bleeding or who received TAE as a prophylactic procedure after the successful endoscopic hemostasis of a high-risk ulcer.

Patients were allocated into two study groups: TAE group (n = 24) and surgical treatment group (n = 43). All patients had high-risk ulcers (Forrest Ia-IIb) of various etiologies. The primary hemostatic method was endoscopic hemostasis. When endoscopy failed, TAE or urgent laparotomy took place. The availability of interventional radiologist and the hemodynamic status of the patient determined the procedure; randomization did not occur.

**Study III**

Study III screened 123 patients undergoing angiography for lower gastrointestinal bleeding during 2004-2016. Out of 123, the study included all 55 patients that received embolization attempt (47 patients with active bleeding and eight patients with negative angiographies). The combination of clinical, endoscopic and imaging findings confirmed the diagnosis of LGIB.
Study IV

Study IV included 49 consecutive patients treated during 2004-2017 for CT-confirmed hepatic tumor hemorrhage independent of tumor etiology. All patients received angiography and embolization attempt. Patients with iatrogenic and traumatic hepatic hemorrhages were excluded.

4.4 STUDY DATA

Electronic medical records provided the study data. The data comprised details on patient demographics, comorbidities, medication, clinical findings, laboratory and imaging results, pathology reports, interventions, complications, follow-up notes and mortality. Death certificates from the Statistics Finland confirmed the time and cause of death.

4.5 INTERVENTIONS

4.5.1 INITIAL EVALUATION AND MANAGEMENT

The initial evaluation and management of all patients took place at the emergency room of the Helsinki University Hospital. The patients received fluid resuscitation and packed red blood cells. Other blood products and medications were sometimes necessary to optimize the clotting status.

Depending on their hemodynamic status and the suspected source of bleeding, the patients underwent upper or lower gastrointestinal endoscopy or CTA to locate the bleeding. CTA replaced invasive catheter angiography in the diagnostics of gastrointestinal bleeding in the Helsinki University Hospital in 2007. Until then, the invasive catheter angiography was the diagnostic method of choice in profuse gastrointestinal bleeding of unknown origin.

Hemodynamically stable patients received TAE in the angio-radiology suite of the radiology unit. Their further follow-up took place at the surgical ward. Hemodynamically unstable patients received TAE in a hybrid operating room that allows for invasive monitoring and the option for rapid conversion to surgery when necessary. The further treatment of unstable patients continued at the intensive care unit (ICU).

4.5.2 STUDY I

The non-surgical management of bleeding pancreatic pseudoaneurysms consisted of a two-step approach that included 1) the controlling of bleeding with TAE in the emergency setting and 2) the management of any remaining
Non-surgical management of bleeding pancreatic pseudoaneurysms by combining transcatheter arterial embolization (TAE) and therapeutic endoscopy. Bleeding splenic artery aneurysm in computerized tomography (CT) scan (1A-B). Splenic artery aneurysm stent exclusion (2A-B). Pancreatic pseudocysts in CT scan six weeks after TAE (3A). Endoscopic pancreatic duct stenting two months after TAE (3B). Pancreatic duct stent and the resolution of pseudocysts in CT scan two months after pancreatic duct stenting (4A-B).
pseudocysts by therapeutic endoscopy at a later stage at outpatient clinic (Figure 8).

**Arterial embolization.** Visualizing the bleeding site in angiography required the selective catheterization of the coeliac, splenic and superior mesenteric arteries. Active contrast extravasation or a filling pseudoaneurysm in angiography necessitated embolization.

**Therapeutic endoscopy.** Any remaining pseudocysts detectable in follow-up CT scan or ultrasound four weeks after TAE necessitated further endoscopic management. This took place approximately four weeks after TAE to avoid potential infection and bleeding complications. Treatment alternatives included transpapillary drainage (pancreatic duct stent) and transmural drainage (pseudocystogastrostomy or pseudocystoduodenostomy). Transmural drainage was the method of choice when the pseudocyst lay adjacent to the gastric or duodenal wall with visible intraluminal bulging. Transpapillary route enabled drainage when the pseudocyst was not in immediate contact with gastric or duodenal wall. When necessary, endoscopic ultrasound was available to locate the pseudocysts during the procedure.

### 4.5.3 STUDY II

**Arterial embolization.** In embolization group, the detection of the bleeding site required catheterizing the coeliac axis and SMA for angiography. Selective angiograms with microcatheters were sometimes necessary. When angiography was positive with extravasation, the bleeding was controlled with coils or particles. When angiography was negative, the patients did not undergo any bleeding provocations. Empirical embolization followed, if the interventional radiologist and surgeon agreed on the most likely bleeding site.

**Surgical treatment.** In surgical group, the hemostatic method of choice was laparotomy with duodenotomy or gastrotomy that allowed the under-running of the bleeding site with or without the ligation of the GDA. Patients requiring emergency resections received gastric wedge resections and ulcer excisions for gastric ulcers and Billroth I resections for duodenal ulcers. None of the patients received truncal vagotomy.

### 4.5.4 STUDY III

The detection of the bleeding site in angiography required the catheterization of the SMA and/or IMA. If the angiography showed no extravasation from these, the catheterization of the internal iliac artery followed. Selective angiograms with microcatheter enabled visualizing the exact bleeding arterial branch. When angiography was positive with extravasation, the
embolization of the bleeding artery with microcoils, particles or gelatine took place as distally as possible – preferably on the level of the vasa recta arteries. Patients did not undergo provocative angiographies after negative angiograms. When the angiogram was negative despite continuous bleeding evident clinically and in CTA, the empirical embolization of the suspected bleeding artery took place in a few complicated cases where laparotomy would have been unfavorable.

4.5.5 STUDY IV

Angiography required catheterizing the hepatic artery. Embolization took place when the angiogram showed extravasation or tumor staining. To preserve as much functioning liver as possible, the preferred level of TAE was the segmental artery level as close to the tumor nidus as technically possible. Lobar TAE, i.e. the embolization of the right or the left hepatic artery, took place only when embolizing segmental arteries would have been insufficient.

4.6 OUTCOMES AND DEFINITIONS

Outcomes

The studied outcomes in all studies included the 30-day rebleeding, complication and mortality rates, the amount of red blood cell transfusions, the durations of ICU and hospital admissions, the incidence of delayed recurrent bleeding and long-term complications, and the estimates of overall survival. Study III included the analysis of factors associated with recurrent bleeding. Study IV included the analysis of factors associated with 30-day mortality.

Definitions

**Technical Success.** The technical success of TAE was defined as technically feasible embolization with post embolization angiogram showing the discontinuation of bleeding. In Study IV, the technical success was defined as the discontinuation of bleeding or as the absence of tumor staining in post embolization angiogram.

**Recurrent Bleeding.** Recurrent bleeding was defined as the recurrence of bleeding symptoms within 30 days of TAE with signs of visible hemorrhage, decreasing hemoglobin level or hemodynamic instability. Delayed recurrent bleeding was defined as the recurrence of bleeding after 30 days of TAE.
**Morbidity.** Post-embolization complications were recorded at 30 days of TAE. They were classified according to Clavien-Dindo Classification [134] in Study I and Study II and according to The Society of Interventional Radiology quality improvement guidelines [59] in Study III and Study IV. Complications classified as “minor” (Clavien-Dindo I) required no more than short observation or nominal therapy and remained insignificant in the follow-up. Complications classified as “major” (Clavien-Dindo II-V) resulted in prolonged hospital admission, increased level of care, permanent adverse outcome, or death.

**Mortality.** Mortality was recorded at 30 days of TAE. Death certificates from Statistics Finland confirmed the time and cause of death.

**Clinical Success of Endoscopic Drainage.** In Study I, the outcomes of therapeutic endoscopy included the complication and mortality rates within 30 days of therapeutic endoscopy. The clinical success of endoscopic drainage was defined as the resolution of pseudocysts in control CT two months after endoscopy. ERCP-related complications defined by Cotton et al. were recorded [135].

### 4.7 STATISTICAL ANALYSIS

IBM SPSS (SPSS Inc., Chicago, IL) enabled the statistical analysis. Percentages summarized categorical data and medians (range) summarized continuous data. The $\chi^2$ test and Fisher's exact test provided the comparison of categorical variables, the Mann-Whitney U test the comparison of continuous variables, and the Linear-by-Linear association test the comparison of ordinal variables. Survival estimates are based on the Kaplan-Meier analysis and survival comparisons on the Breslow's test. The Cox regression analysis yielded hazard ratios for survival comparison between the study groups in Study II. Univariate binary logistic regression allowed the analysis of factors associated with the 30-day recurrent bleeding in Study III and the 30-day mortality in Study IV. Two-tailed tests gave the $P$ values that were considered statistically significant when less than 0.05.

### 4.8 ETHICAL APPROVAL AND PERMISSIONS

The Helsinki University Hospital Research Board granted the study approval for each study separately. The Finnish law allows conducting retrospective research from hospital medical records without patient approval. Thus, informed patient consent and ethical approval were not necessary.
5 RESULTS

5.1 STUDY I

During 2004-2014, bleeding pancreatic pseudoaneurysms necessitated angiography and embolization in 58 patients with underlying pancreatitis (48 male and 10 female) (Table 4). The most common etiology of pancreatitis was alcohol in 88% of patients. The main complaints at presentation were abdominal pain (71%), melena (29%) and hematemesis (21%), with 7% of the patients being hemodynamically unstable. In CT/CTA imaging, 55 patients had a pseudocyst and 49 patients had a pseudoaneurysm. The median diameters of the pseudocysts and pseudoaneurysms were 5.9 cm (2.4-42) and 2.1 cm (0.6-8.4), respectively. According to CT scan, active bleeding was suspected in 51 patients (90%).

5.1.1 TRANSCATHETER ARTERIAL EMBOLIZATION

Median time from admission angiography was 18 hours (0-266). Angiography showed active extravasation in 50 patients (86%). The most common bleeding artery was the splenic artery (52%), followed by the GDA (19%) and the gastroepiploic artery (9%).

Embolization was technically feasible in all 58 patients (100%). When angiography was negative, CT findings enabled targeting the empirical embolization of the most likely bleeding artery. The most common embolization method used was coiling (90%), followed by stents (5%), particles (3%) and plugs (2%).

Recurrent Bleeding

The 30-day rebleeding rate was 16%, nine patients developing recurrent bleeding (Table 5). Out of nine, seven patients underwent repeated angiography and embolization and two patients required surgery. The overall success rate of TAE after re-embolizations was 97%, with only two patients requiring surgical management.

Complications

The 30-day complication rate was 31%, with post-embolization complications diagnosed in 18 patients. The most common complication was CT-verified splenic infarction, occurring 50% of patients receiving splenic artery embolization. A large infarction or the necrosis of the whole spleen was
Table 4  
**Demographic details and baseline characteristics of patients undergoing transcatheter arterial embolization for gastrointestinal bleeding**

|                      | Study I  
|----------------------|------------
|                      | (n = 58)   | Study II  
|                      |            | TAE (n = 24) | ST (n = 43) | Study III  
|                      |            |             |             | (n = 53) | Study IV  
|                      |            |             |             | (n = 45) |
| Age, median (range)  | 55 (26-73) | 68 (38-85)  | 67 (28-91)  | 72 (30-95) | 69 (28-88) |
| Sex, male, n (%)     | 48 (83)    | 16 (67)     | 26 (61)     | 37 (70)    | 31 (69)    |
| CACI                 | 4 (1-11)   | 5 (1-12)    | 5 (1-9)     | 7 (0-12)   |             |
| Anticoagulant use, n (%) | 9 (38) | 17 (40)     | 32 (60)     | 18 (40)    |             |

**Symptoms**

|                  | Study I  
|------------------|------------
|                  | (n = 58)   | Study II  
|                  |            | TAE (n = 24) | ST (n = 43) | Study III  
|                  |            |             |             | (n = 53) | Study IV  
|                  |            |             |             | (n = 45) |
| Hematemesis, n (%) | 12 (21) | 9 (38)      | 26 (61)     | 0 (0)      | 1 (2)      |
| Melena, n (%)      | 17 (29)    | 19 (79)     | 29 (67)     | 12 (23)    | 2 (4)      |
| Hematochezia, n (%) |         |             |             | 49 (93)    | 0 (0)      |
| Abdominal pain, n (%) | 41 (71) | 5 (21)      | 12 (28)     | 6 (11)     | 40 (89)    |
| Preceding collapse, n (%) | 4 (17) | 13 (30)     | 13 (30)     | 5 (9)      | 2 (4)      |

**Findings on admission**

|                  | Study I  
|------------------|------------
|                  | (n = 58)   | Study II  
|                  |            | TAE (n = 24) | ST (n = 43) | Study III  
|                  |            |             |             | (n = 53) | Study IV  
|                  |            |             |             | (n = 45) |
| Hemoglobin (g/l)  | 98 (31-152) | 70 (39-122) | 67 (28-100) | 84 (33-147) | 79 (51-119) |
| Coagulopathy, n (%) | 9 (16) | 8 (33)      | 12 (28)     | 18 (40)    | 21 (49)    |
| Shock, n (%)       | 4 (7)      | 6 (25)      | 14 (33)     | 13 (29)    | 15 (31)    |
| Abdominal distention, n (%) | 33 (57) | 1 (4)      |             | 35 (78)    |             |
| Hematemesis, n (%) | 5 (9)    | 8 (33)      | 22 (51)     | 0 (0)      | 0 (0)      |
| Melena, n (%)      | 16 (28)    | 22 (92)     | 34 (79)     | 10 (19)    | 2 (4)      |
| Hematochezia, n (%) |         |             |             | 49 (93)    | 0 (0)      |

CACI: Charlson Age Comorbidity Index, ST: Surgical treatment, TAE: Transcatheter arterial embolization

*TT% < 50 and/or platelet count < 50 E9/l

**Systolic blood pressure < 90 mmHg

*No statistically significant difference between study groups (X² test, Fisher’s exact test, Mann-Whitney U test > 0.05)
Table 5  The 30-day results of transcatheter arterial embolization in gastrointestinal bleeding

<table>
<thead>
<tr>
<th></th>
<th>Study I (n = 58)</th>
<th>Study II TAE (n = 24)</th>
<th>Study III ST (n = 43)</th>
<th>Study IV (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent bleeding, n (%) (^b)</td>
<td>9 (16)</td>
<td>6 (25)</td>
<td>7 (16)</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Complication rate, n (%)</td>
<td>18 (31)</td>
<td>9 (38)</td>
<td>29 (67) (^a)</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Major, n (%) (^c)</td>
<td>8 (14)</td>
<td>5 (21)</td>
<td>20 (47)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Minor, n (%) (^d)</td>
<td>10 (17)</td>
<td>4 (17)</td>
<td>9 (21)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Mortality rate, n (%)</td>
<td>2 (3)</td>
<td>3 (13)</td>
<td>11 (26)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Blood transfusions, units of RBCs, median (range)</td>
<td>4 (0-28)</td>
<td>24 (6-37)</td>
<td>19 (6-54)</td>
<td>12 (2-58)</td>
</tr>
<tr>
<td>Duration of ICU treatment, days, median (range)</td>
<td>0 (0-13)</td>
<td>0 (0-7)</td>
<td>0 (0-17)</td>
<td>0 (0-6)</td>
</tr>
<tr>
<td>Duration of hospital stay, days, median (range)</td>
<td>3 (0-27)</td>
<td>11 (5-39)</td>
<td>11 (2-43)</td>
<td>7 (1-91)</td>
</tr>
</tbody>
</table>

\(^a\) Technically feasible embolization with post-embolization angiogram showing the discontinuation of bleeding
\(^b\) Recurrence of bleeding symptoms within 30 days of embolization
\(^c\) Complication resulting in prolonged hospital stay, increased level of care, permanent adverse outcome, or death
\(^d\) Complication requiring no more than short observation or nominal therapy

ICU Intensive care unit; RBC Red blood cell

\(^e\) \(P = 0.018 \) (\(X^2\) test)
detectable in seven patients. The drainage of splenic necrotic abscess was necessary in three of these. After splenic artery embolization, the follow-up CT at one year showed asplenia in two patients (7%). The first patient had undergone the drainage of a large splenic necrotic collection after TAE, whereas the other patient had experienced an uneventful post-embolization recovery (Figure 9). After the embolization of the GDA, one patient developed upper abdominal pain and transient duodenal mucosal ischemia detectable in post-embolization upper endoscopy.

**Mortality**

The mortality rate was 3%, two patients dying within 30 days of embolization. One patient died on the operating table of disseminated intravascular coagulopathy and profuse bleeding. Another patient had chronic obstructive pulmonary disease and died of pneumonia and acute respiratory distress syndrome eight days after TAE.

**Other Outcomes**

The median need for blood transfusions was four units of packed RBCs (0-28). The median duration of ICU treatment was 0 days (0-13). Discharge from the hospital was possible after a median of three days (0-27). The incidence of delayed recurrent bleeding was 2%. The recanalization of a hepatic artery aneurysm necessitated repeated TAE 41 weeks after the primary procedure.

### 5.1.2 THERAPEUTIC ENDOSCOPY

The initial CT scan showed a pancreatic pseudocyst in 55 out of 58 patients. Out of 55, 47 patients received follow-up and treatment for their pseudocysts in the Helsinki University Hospital. Thus, the analysis of the safety and efficacy of therapeutic endoscopy in the treatment of bleeding pancreatic pseudocysts included 47 patients.

**Clinical Success**

Follow-up imaging after TAE showed the spontaneous resolution of the pseudocysts in 13 out of 47 patients (28%). The remaining 34 patients received endoscopic treatment attempt. Out of 34, two patients had unsuccessful cannulation (6%) and 32 patients underwent endoscopic drainage. Transpapillary drainage with pancreatic duct stent was the most common method used in 75% of patients. Transmural drainage methods included pseudocystogastrostomy and pseudocystoduodenostomy in 22%
Figure 9  Ischemia and the complete resorption of spleen following the transcatheter arterial embolization (TAE) of splenic artery. Bleeding pseudoaneurysm in the body of pancreas in computerized tomography angiography (1A-B). Coil-embolization of splenic artery with uneventful recovery (2A-B). Endoscopic management of pancreatic pseudocyst with pancreatic duct stent (3A-B). Asplenia in computerized tomography scan a year after TAE (4A-B).
and 3% of patients, respectively. Of the 32 patients with initially successful endoscopy, seven patients (22%) required additional drainage procedures (six non-surgical and one surgical). Including the pseudocysts that resolved spontaneously, the overall success rate of the non-surgical management of pancreatic pseudocysts was 91%.

**Complications**
The 30-day complication rate was 21%, seven patients developing complications after the endoscopic management. Pseudocyst infection was the most common complication occurring in four patients (12%), followed by pseudocyst hemorrhage in two (6%) and post-ERCP pancreatitis in one (3%). All patients with pseudocyst infection received a prophylactic antibiotic before the endoscopic procedure. Pseudocyst hemorrhage necessitated TAE in one and surgery in the other patient. Post-ERCP pancreatitis was of mild course and resolved spontaneously.

**Mortality**
The 30-day mortality after ERCP was 3%, one patient dying of unknown cause 29 days after the procedure. By the time of data retrieval after a median follow-up of 15 months (1-75), 23 out of 58 study patients were dead. The most common cause of death was alcohol liver disease (30%) followed by cancer (13%). Chronic pancreatitis was the cause of death in one patient (4%).

### 5.2 STUDY II

During 2000-2015, active or recurrent UGIB after failed endoscopic hemostasis necessitated TAE in 24 patients and surgical management in 43 patients (Table 4). Patients with active bleeding despite endoscopic treatment attempt were more likely to undergo surgery than patients with recurrent bleeding after initially successful endoscopy (65% vs. 35%, \( P = 0.005 \)). Other baseline characteristics did not differ between the groups. The most common ulcer etiology in both study groups was peptic ulcer disease (TAE group 92%, surgery group 88%), followed by malignant ulcers (TAE group 4%, surgery group 5%).

**Interventions**
The TAE group received a median of two (0-5) endoscopic treatment attempts and the surgery group received one (0-5) endoscopic treatment attempt before the secondary hemostatic procedure (\( P = 0.908 \)). The median time from admission to the secondary hemostatic procedure was longer in
Results

TAE group than in surgery group (59 hours (2-556) vs. 19 hours (1-721), \( P = 0.023 \)).

Embolization group underwent 17 coil embolizations, three particle injections and two combined procedures with coils and particles. The most common bleeding artery was the GDA in 67% of patients, followed by the left gastric artery in 13% of patients. Due to negative angiography, TAE was not feasible in two patients (8%). These two required surgical treatment but were analyzed within their initial study group due to the intention-to-treat principle.

Surgical group underwent 43 laparotomies. The most common procedure was under-running of the bleeding ulcer through duodenotomy in 23 patients and through gastrotomy in 16 patients. Out of 43, four patients required gastric resection.

Recurrent Bleeding

The 30-day rebleeding rate was 25% after TAE and 16% after surgery (\( P = 0.641 \)) (Table 5). In TAE group, six patients developed recurrent bleeding. Out of six, two patients underwent repeated TAE, two patients underwent laparotomy and gastric wedge resection, one patient underwent endoscopic hemostasis, and one patient died of bleeding recurrence after discharge from the hospital. In surgery group, seven patients developed recurrent bleeding. Out of seven, four patients received successful TAE, two patients underwent re-laparotomies with gastric wedge resections, and one patient died of bleeding before further procedures. Patients rebled within a median of one day (0-17) from the primary procedure. Delayed recurrent bleeding did not occur.

Complications

Post-operative complications were less frequent after TAE than surgery. The 30-day complication rate was 38% after TAE and 67% after surgery (\( P = 0.018 \)). Post-operative complications occurred in nine patients after TAE (major complications in five) and in 29 patients after surgery (major complications in 20). The incidence of major complications did not differ between TAE and surgery (25% vs. 44%, \( P = 0.196 \)). Post-operative ICU treatment was necessary in 33% of patients after TAE and in 47% of patients after surgery (\( P = 0.294 \)).

In TAE group, major complications included acute renal failure and dialysis three patients (13%), massive pulmonary embolism in two patients (8%), and iliac artery thrombosis with lower limb ischemia in one patient (4%). Minor complications included endoscopy-verified self-limiting ischemic mucosal changes in the antrum or duodenum in three patients (13%). None of them developed pyloric or duodenal stenosis during the follow-up. Only one patient required surgery for a complication after TAE:
The thrombosis of the right iliac artery following femoral cannulation necessitated revascularization in an arteriosclerotic patient a week after TAE. In surgery group, major complications included aspiration pneumonia and sepsis in seven (16%), anastomotic leakage in three (7%), wound dehiscence in one (2%), acute renal failure and dialysis in two (5%), myocardial infarction in two (5%), bleeding-induced lower limb ischemia in one (2%), pneumothorax in one (2%), catheter sepsis in one (2%), and cardiac insufficiency and respiratory failure in two patients (5%). Minor complications comprised delirium or cognitive impairment without intracranial CT findings in four (9%), pulmonary embolism in one (2%), pneumonia in two (5%), pleural effusion in one (2%), and paralytic ileus in one patient (2%). In surgical group, post-operative complications necessitated interventions under general anesthesia in five patients (12%). Out of five, three patients had a leakage. The leakage necessitated duodenal stenting in one patient whereas two patients died of complications after several re-laparotomies. Wound dehiscence necessitated re-laparotomy in one patient. Amputation due to bleeding- and hypoperfusion-induced lower limb ischemia was necessary in one patient with underlying arteriosclerosis.

**Angiography-related peri-operative complications** included arterial wall perforation with contrast extravasation in four patients, arterial wall dissection in two patients, coil misplacement in one patient, and iliac artery thrombosis after the cannulation of the right femoral artery in one patient. Iatrogenic extravasation necessitated additional coiling in three patients. The iatrogenic dissection of the SMA in one patient did not require further procedures: the SMA remained patent in the follow-up. The thrombosis of the right iliac artery following femoral cannulation necessitated surgical revascularization. Iliac artery stenting would have enabled the immediate treatment of the complication, had the thrombosis been diagnosed in the initial angiography.

**Mortality and Overall Survival**

The 30-day mortality rates did not differ between TAE and surgery (13% vs. 26%, \( P = 0.347 \)). After TAE, three patients died. The causes of death included recurrent bleeding, pulmonary embolism, and aspiration pneumonia with sepsis and multiple organ failure. After surgery, eleven patients died. The causes of death included aspiration pneumonia and sepsis in five patients, cardiopulmonary complications in four patients, anastomotic leakage in one patient, and recurrent bleeding in one patient.

Mortality at one year was not associated with the treatment approach (HR (TAE vs. surgery) = 1.205 (95% CI 0.537-2.705, \( P = 0.651 \)). The mean overall survival estimate was 91 months (95% CI 52-131) after TAE and 35 months (95% CI 5-66) after surgery (\( P = 0.230 \)). The 1-year survival estimates after TAE and surgery were 70% (95% CI 51-89) and 59% (95% CI 43-74), respectively.
Results

Other Outcomes

The median requirement for blood transfusions was 24 units (6-37) of packed RBCs in the TAE group and 19 units (6-54) of packed RBCs in the surgery group ($P = 0.06$). The median duration of ICU treatment was 0 days (0-7) in the TAE group and 0 days (0-17) in the surgery group ($P = 0.553$). The median duration of hospital admission was 11 days (5-39) in the TAE group and 11 days (2-43) in the surgery group ($P = 0.477$).

5.3 STUDY III

During 2004-2016, 55 patients with LGIB received angiography and embolization attempt. The median time from hospital admission to angiography was nine hours (0-330). Angiography showed active bleeding in 47 patients and remained negative in eight patients. It located the bleeding in the small bowel in 23%, in caecum and right hemicolon in 15%, in transverse colon in 10%, in left hemicolon and sigmoid in 26%, and in rectum in 26% of patients. The branches of the SMA and IMA were the source of bleeding in 47% and 45% of patients, respectively. The remaining 8% of the bleeding episodes originated in the internal iliac artery.

Embolization was technically feasible in 53 patients (96%) (Table 4). The most common embolization method was microcoils either alone (62%) or combined with particles (11%) or gelatine (6%).

**Empirical embolization.** Out of 53, eight patients received empirical embolization after negative angiography. All eight patients had active bleeding and were considered poor candidates for emergency surgery. A preceding positive CTA facilitated targeting the embolization in five patients and metallic clips inserted during endoscopy in one patient. The remaining two had rectal malignancies – the first was waiting for definitive surgical management after chemoradiation while the other had a locally advanced disease with rectovesical fistula.

The most common etiology of bleeding was diverticular disease in 39% of patients, followed by post polypectomy hemorrhage in 13% and malignant tumors in 11% of patients. No definitive diagnosis could be established in ten patients (19%).

Recurrent Bleeding

The 30-day rebleeding rate was 26%, 14 patients experiencing recurrent bleeding (Table 5). Out of 14, seven patients underwent re-intervention (five surgical, one TAE and one endoscopic), six experienced the spontaneous resolution of bleeding and one died. Recurrent bleeding occurred within a median of two days (0-18) of TAE. The higher need of blood transfusions was associated with 30-day rebleeding in logistic regression analysis (HR 1.12, 95% CI 1.01-1.24, $P = 0.032$). Age, gender, anticoagulant medication,
hemoglobin level at presentation, hypovolemic shock or coagulopathy at presentation, time to embolization, and underlying etiology were not associated with early recurrent bleeding.

**Empirical embolization.** After empirical TAE, recurrent bleeding occurred in three patients (38%) and resolved spontaneously in all of them. The 30-day rebleeding rate of empirical TAE did not differ from the 30-day rebleeding rate of TAE with positive angiography ($P = 0.422$).

**Complications**

The 30-day complication rate was 36%, 19 patients developing post embolization complications. Major complications occurred in nine patients (17%) and comprised bowel ischemia in six patients (11%), catheter-induced bowel wall perforation in one patient (2%) and ischemic colitis in two patients (4%). Six patients with a major complication required surgery during the same hospital admission – five for bowel ischemia and one for catheter-induced mechanical bowel perforation. Two patients with post embolization ischemic colitis underwent initially successful non-surgical management: One patient with sepsis and endocarditis received medical management. The other recovered spontaneously but developed ischemic strictures and had to undergo laparotomy two months later due to iatrogenic bowel perforation following balloon dilatation. Post-embolization rectal ischemia caused the death of a patient with end-stage endometrial cancer.

Minor complications occurred in ten patients (19%) and comprised self-limiting ischemic colitis in three patients (6%), post-embolization abdominal pain in three patients (6%), puncture site hematoma in two patients (4%), pneumonia in one patient (2%), and angina pectoris in one patient with underlying coronary heart disease (2%). The overall incidence of ischemic complications, minor and major, was 17%.

**Angiography-related peri-operative complications** occurred during seven embolizations and included three coil misplacements, one arterial dissection, one arterial perforation and an episode of perioperative abdominal pain. None of these required further interventions and all remained clinically insignificant.

**Mortality and Overall Survival**

The mortality rate was 6%, three patients dying within 30 days of TAE. The causes of death comprised profuse bleeding in a patient with warfarin overdose, exacerbation of underlying medical conditions after the successful controlling of bleeding in a patient with multiple comorbidities, and rectal ischemia in a patient with end-stage endometrial carcinoma invading the rectum.

The 1-year and 5-year survival estimates were 79% (95% CI 68-91) and 49% (95% CI 33-65), respectively. After a median follow-up of 26 months (0-
174), 49% of patients were dead. The most common causes of death were neurological disorders (27%), malignancies (19%) and cardiovascular diseases (15%).

**Other Outcomes**
The median need for blood transfusions was 12 units (2-58) of packed RBCs. The median duration of ICU admission was 0 days (0-6). Discharge from the hospital was possible after a median of seven days (1-91). During the follow-up, delayed recurrent bleeding occurred in two patients (4%) and ischemic colonic stricture in one patient (2%).

### 5.4 STUDY IV

During 2004-2017, angiography was necessary due to hepatic tumor hemorrhage in 49 patients (34 male and 15 female) (unpublished results). Embolization was technically feasible in 45 patients (92%), 44 patients receiving TAE and one undergoing arterial chemoembolization in the acute setting (Table 4). The most common embolization method was the combination of coils and particles (56%), followed by particles only (29%). Embolization in the segmental artery level was possible in 39 patients (87%), whereas lobar embolization in the level of the right or left hepatic artery was necessary in six (13%).

**Recurrent Bleeding**
The 30-day rebleeding rate was 16%, recurrent bleeding occurring in seven patients (Table 5). Out of seven, three patients underwent repeated TAE and two received end-of-life care. Bleeding resolved spontaneously in two patients managed expectantly with fluid resuscitation and blood transfusions.

**Complications**
The 30-day complication rate was 57%, 15 patients (33%) developing major and 11 patients (24%) minor complications. The most common major complication was renal, hepatic, hepatorenal or multiorgan failure in 16% of patients, followed by post-embolization hepatic tumor necrosis and abscess in 4%, cardiopulmonary complications in 4% and bacteremia in 4% of patients. Minor complications included unspecified fever (11%), delirium (4%), pneumonia (2%), atrial fibrillation (2%), cardiac insufficiency (2%), and puncture site hematoma (2%).

**Angiography-related peri-operative complications** occurred in seven patients (16%) and included non-target embolization, arterial
dissection, and the perforation of the arterial wall. All of these remained clinically insignificant.

**Mortality and Overall Survival**

The mortality rate was 33%. Out of 45, 15 patients died within 30 days TAE. The immediate causes of death included acute hepatic or renal failure in seven patients, continuous hemorrhage in four, gradual decline after acute hemorrhage in two, and bleeding from esophageal varices in one.

In hospital—mortality in the whole study population was 29%, 14 patients dying during the same hospital admission. In-hospital mortality was significantly higher among cirrhotic than non-cirrhotic patients (55% vs. 7%, $P < 0.001$).

The median overall survival estimate was 93 days (95% CI 21-165). The overall survival was worse among cirrhotic than non-cirrhotic patients (12 d (95% CI 0-27) vs. 175 d (95% CI 72-278), $P = 0.037$).

Out of 49, 46 patients (94%) were dead after a median follow-up time of 3.6 months (0-112.6). The most common causes of death comprised hepatocellular cancer (64%), other malignancies (16%) and cirrhosis (16%). The study included three patients with HCA. They were all women between 20-40 years of age. At the end of the follow-up, two were alive and one had died of a chronic neurological disease.

**Other Outcomes**

The median need for blood transfusions was five units (0-12) of RBCs. The median durations of ICU and hospital admissions were 0 days (0-8) and 11 days (1-18), respectively. As further management, 12 patients (24%) received chemotherapy, five received transcatheter arterial chemoembolization (TACE) (10%), and five (10%) underwent staged liver resection.
6 DISCUSSION

6.1 EFFICACY OF ARTERIAL EMBOLIZATION

Arterial embolization was efficient in controlling the bleeding with the first attempt in 84% of patients with bleeding pancreatic pseudoaneurysms, in 75% of patients with UGIB, in 74% of patients with LGIB and in 84% of patients in hepatic tumor hemorrhage. The results are consistent with findings from earlier studies, showing 30-day rebleeding rates of 4-14% in pancreatic pseudocysts [21,22,110,111], 15-46.7% in UGIB, 5-24% in LGIB [79,97-99] and in 6-20% in hepatic tumor hemorrhage [24,114,115].

The majority of the episodes of recurrent bleeding resolved spontaneously or after repeated TAE. Recurrent bleeding necessitated surgery in two out of 58 patients (3%) with bleeding pancreatic pseudoaneurysms, in two out of 24 patients (10%) with UGIB, and in five out of 53 patients (9%) with LGIB. Out of 45 patients with hepatic tumor hemorrhage, seven developed recurrent bleeding but none of them underwent emergency surgery.

To study the current role of surgery in the treatment of gastrointestinal bleeding, Köhler at al. analyzed 54 consecutive patients undergoing TAE for LGIB (25 patients), UGIB (17 patients) and intra-abdominal or retroperitoneal bleeding (13 patients) [136]. Out of 54, 11 patients (20%) required surgery after TAE – five patients (9%) for early rebleeding (≤ 30 d) and two patients (4%) for delayed rebleeding, post-embolization complications, and the consequences of bleeding, respectively. The authors concluded that surgery has lost its importance as the initial therapy of gastrointestinal bleeding but continues to play an important role in the management of early and delayed rebleeding and TAE- and bleeding-related complications.

In current as well as in earlier studies, the 30-day rebleeding rates are the highest after embolizations for UGIB. The complex blood supply in the area with rich collateral vasculature is one likely explanation. A meta-analysis from Mirsadraee et al. (2011) listed coagulopathy and the use of coils as the only embolic material as predictors of early recurrent bleeding in UGIB [78]. Correcting the coagulation status of all bleeding patients before TAE is of utmost importance. Since coils elicit vessel occlusion through thrombosis, coils alone may not be a sufficient embolization method in coagulopathic patients with UGIB.

6.2 SAFETY OF ARTERIAL EMBOLIZATION

In current study, the 30-day mortality rates after TAE for bleeding pancreatic pseudoaneurysms, UGIB, LGIB and hepatic tumor hemorrhage were 3%,
13%, 6% and 31%, respectively. The 30-day complication rates were 31%, 38%, 36% and 57%, correspondingly. Post-embolization complications required surgical management in one patient (2%) with pancreatic pseudoaneurysms, in one patient (4%) with UGIB, in eight patients (15%) with LGIB, and in one patient (2%) with hepatic tumor hemorrhage. Surgery-requiring complications in the whole study population included colon pseudo-obstruction after massive bleeding from a pancreatic pseudoaneurysm in Study I, iliac artery thrombosis and lower limb ischemia in Study II, catheter-induced bowel wall perforation in one patient and bowel wall ischemia in seven patients in Study III, and hepatic necrosis and abscess in Study IV.

In general, arterial embolization is a safe approach above the ligament of Treitz. In this area of rich collateral vasculature, ischemic complications are rare and usually self-limiting. Ischemic pyloric and duodenal stenosis are potential concerns after the embolization of the GDA in UGIB [2]. In pancreatic pseudoaneurysms, the embolization of pancreaticoduodenal artery may lead in gallbladder wall ischemia that necessitated cholecystectomy in two patients in the series of Köhler et al. (2014) [136]. In current study, duodenal stenosis or gallbladder necrosis did not occur.

The embolizations of splenic artery pseudoaneurysms carry a risk of splenic ischemia. In current study, it occurred in 50% of patients (15 out of 30), necrotic splenic abscess requiring antibiotic treatment with or without drainage in seven patients. The study on the endovascular management of pancreatitis-related bleeding by Kim et al. (2015) shows a similar pattern: eight out of 16 patients (50%) developed splenic ischemia, necrotic splenic abscess requiring antibiotics and percutaneous drainage in three patients [111].

Earlier studies show preserved splenic immune function following splenic artery embolization [16,107]. The patients in current study did not receive routine vaccinations after the procedure. However, the necrotic spleen got fully resorbed in two patients (7%), a CT scan a year later showing asplenia. Patients with post-embolization asplenia should be provided with post-splenectomy immunizations. Thus, especially when extensive splenic necrosis occurs, a follow-up CT scan to detect possible asplenia is worth considering.

The dual blood supply of the liver allows the embolization of the hepatic artery branches with a minimal risk of parenchymal ischemia when the portal vein is patent. The exact incidence of tumor necroses and abscesses after embolization for hepatic tumor hemorrhage is poorly documented. In present study, they occurred in 9% of patients (four out of 45) and resolved with antibiotics in all but one.

Supported by earlier studies, the essential finding of current study was the poor survival of cirrhotic HCC patients undergoing embolization for hepatic tumor hemorrhage. It remains a clinical challenge to differentiate the patients with cirrhosis that, instead of invasive procedures, would rather...
benefit from the right-timed and good-quality end-of-life care. At least four earlier studies report no survival benefit from TAE in cirrhotic patients with bilirubin level over 50 µmol/l, and some authors do not recommend TAE in cirrhotic patients with bilirubin levels above this cut-off value [113]. Due to the small study population, current study was not able to establish any cut-off values or study the associations between the different stages of cirrhosis and the 30-day mortality.

Despite super-selective techniques in embolization for LGIB, ischemic complications remain a significant concern. Current study shows major ischemia in 15% of patients, whereas earlier studies report ischemia (minor and major) in 0-13% [97-99,101]. The higher ischemia rate in present study may be attributable to embolizations less selective than optimal: in retrospective review, the angiograms of patients with major ischemia show coils in two or three parallel vasa recta vessels and additional coils even in the level of marginal artery in two patients (Figure 4, Figure 7). This finding highlights the importance of performing the embolization as selectively as possible on the vasa recta level only. Köhler et al. (2014) recommend occluding no more than two adjacent vasa recta arteries at a time [136]. Before embolization for LGIB, a thorough pre-operative patient counselling on the potential risks and benefits is important.

Angiography- and embolization-related peri-operative complications occurred with a notable frequency. The most severe complication related to femoral artery puncture was the thrombosis of the iliac artery in a patient with underlying arteriosclerosis, necessitating surgical revascularization a week after TAE. Iliac artery thrombosis is a rare but recognized complication of angiography [137]. Had the thrombosis been noticed in the initial angiography, iliac artery stenting would have enabled the immediate treatment of the complication. The more common complications included catheter-induced arterial wall perforations, arterial dissections, non-target embolizations, and coil migration through duodenal mucosa after the embolization of the GDA. All of these were successfully controlled during the procedure and remained clinically insignificant.

6.3 FEASIBILITY OF ARTERIAL EMBOLIZATION

Technical Feasibility of Arterial Embolization

In current study, the technical feasibility TAE in gastrointestinal bleeding was very high regardless of the origin of bleeding. The technical success rates varied from 92% in UGIB and spontaneous hepatic hemorrhage to 96% in LGIB and 100% in pancreatic pseudoaneurysms. Previous studies report technical success rates of 89-100% in UGIB [8,71,72,74,86], 85-100% in LGIB [98,99,104,138], 82-100% in bleeding pancreatic pseudoaneurysms [111,139] and 91-100% in hepatic tumor hemorrhage [114,115,140].
The adoption of CTA in the diagnostics of LGIB in the Helsinki University Hospital in 2007 markedly increased the rate of angiographies leading to successful embolization (27% before 2007 vs. 64% after 2007, \( P < 0.001 \)). Despite this, negative angiography was the most common reason to refrain from embolization in current study. A negative angiography that neither identifies the source of bleeding nor allows TAE as a therapeutic intervention – and yet predisposes the patient to complications of an invasive procedure – is a frustrating finding for a clinician. This is the case especially, when the patient clearly shows symptoms of continuous bleeding.

Angiography may fail to show active bleeding due to various reasons. Such reasons may include scant bleeding that does not reach the sensitivity of angiography, intermittent bleeding, variant perfusion patterns, or bleeding of venous origin. Hemodynamic instability correlates with positive angiography, and some authors have suggested the thresholds of 1) systolic blood pressure less than 100 mmHg, 2) heart rate over 100 beats per minute, and 3) blood transfusion requirement of over four units of RBCs in 24 hours to guide the decision to proceed to angiographic evaluation [141]. Initial CTA before angiography may help localize the bleeding, show its cause, and direct the angiographic evaluation.

Provocative mesenteric angiography refers to the use of anticoagulant, thrombolytic and vasodilating medication to elicit bleeding from a source that has recently stopped bleeding. Kim et al. (2010) studied the safety and efficacy of provocative angiography in recurrent LGIB with initially negative angiography [95]. Their study protocol included the administration of intravenous heparin to provoke bleeding and intra-arterial nitroglycerin for vasodilation after the selective catheterization of the suspected artery. If the angiography remained negative, the selective intra-arterial injection of tissue plasminogen activator (alteplase) followed. Provocative angiography enabled the identification of bleeding site in 12 out of 36 initially negative angiographies (33%) without any bleeding complications.

Kamo et al. (2016) described provocative endoscopy to identify bleeding site after initially negative angiography in three patients with UGIB [142]. With catheters left in place after the selective catheterization of GDA, patients underwent provocative endoscopy in the interventional radiology suite. Endoscopic removal of visible blood clot elicited active bleeding, enabling the endovascular controlling of hemorrhage. The procedure was technically feasible and controlled the bleeding in all three patients. No bleeding complications occurred. Endoscopically visible hemorrhage is usually amenable to endoscopic management with e.g. fibrin glue, metallic clips or hemostatic powder. To facilitate embolization, endoscopic marking of the ulcer with a metallic clip is a safe alternative to endoscopic bleeding provocation [70]. However, the provocative endoscopy during angiography may be a useful approach when various reasons such as the difficult location of bleeding or profuse bleeding after clot removal render endoscopic management inaccessible.
Provocative techniques require co-operation between the referring clinician and the interventional radiologist. In pharmaceutical bleeding provocations, the patient should not have any contraindications to anticoagulants or thrombolytic agents. Although major complications seem rare, provocative techniques have not become routine practise, and they were not exploited in current study either. The underlying reasons are likely to relate to the fear of bleeding complications and to clinicians and interventional radiologists being unfamiliar with the technique [95]. However, provocative techniques should not be forgotten, and they may be a useful tool especially in detecting intermittent and occult gastrointestinal bleeding [143].

Traditional invasive catheter angiography is contraindicated in life-threatening iodine allergy. Renal insufficiency is a relative contraindication, although hemodynamic instability often justifies the use of iodine contrast agents in the emergency setting. Alternative pre-angiography imaging methods like MRI and contrast agents like carbon dioxide may sometimes be useful especially in patients with iodine allergy [144].

**Availability of Arterial Embolization**

Current study shows a clear shift from surgery to arterial embolization in the emergency management of gastrointestinal bleeding in the Helsinki University Hospital over the last two decades. During 2004-2014, bleeding pancreatic pseudoaneurysms of any etiology necessitated hemostatic interventions in 74 patients with only eight of them (11%) receiving upfront surgery as the primary intervention. During 2000-2015, UGIB necessitated TAE or surgery in 85 patients. The proportion of embolizations increased significantly during the second half of the study period (24% in 2000-2007 vs. 52% in 2008-2015, \( P = 0.018 \)). According to current guidelines, arterial embolization is the preferred first-line intervention in bleeding pancreatic pseudoaneurysms and hepatic tumor hemorrhage [23,50]. It is the recommended second-line treatment modality after failed endoscopic hemostasis also in LGIB and UGIB [88,92]. Despite this, factors other than surgical risk may direct the decision-making between TAE and surgery. Such factors include e.g. the availability of services from interventional radiologists [6,75].

Study II shows that surgery offered a faster hemostasis in UGIB during the study period in the Helsinki University Hospital: Surgical patients had active bleeding in endoscopy more often than TAE patients who received more endoscopic treatment attempts and had longer waiting times for the salvage procedure. The same trend was evident also in the national audit on TAE and surgery in treatment of UGIB in United Kingdom in 2007 [6]. The study showed that patients undergoing surgery were older and more likely to present with shock or hematemesis, have coagulopathy and lower hemoglobin level on admission, and receive fewer endoscopic treatment
attempts than patients undergoing TAE. The authors concluded this to reflect the availability of interventional radiology services in United Kingdom at the time of the audit.

Access to embolization is limited in secondary referral hospitals also in Finland, and regional inequality exists in terms of access to treatment. In current study, 34-62% of patients, depending on the bleeding site, received referral for TAE in the Helsinki University Hospital from other hospitals. The availability of TAE varies also depending on the time of day, the majority of angiographies in current study taking place during daytime (58% between 8 am – 4 pm, 34% between 4 pm and midnight, 8% between midnight and 8 am). In Study II comparing TAE and surgery in UGIB, all hemostatic interventions taking place at nighttime between 8 pm and 8 am were surgeries.

Is the limited availability of TAE likely to cause increased mortality in patients presenting with gastrointestinal bleeding outside tertiary referral hospitals or regular working hours? To study the weekend effect in UGIB-related mortality in United Kingdom, a nationwide study included 6750 patients from 212 hospitals and compared the treatment outcomes between patients admitted during the weekdays and weekends [145]. The results did not show any association between weekend admission and mortality, although patients admitted during the weekend were more likely to present with shock and had significantly longer delays to endoscopy. Neither did the odds for mortality differ in patients treated in centers with a 24-hour endoscopy rota compared to centers without one. As the authors concluded, prompt resuscitation and stabilization procedures seem to be the most important aspects of clinical care. It is likely that establishing a 24-hour rota for interventional radiologists would not automatically be associated with lower mortality in bleeding patients either.

6.4 STRENGTHS AND LIMITATIONS OF THE STUDY

Each study included patients over a period ten years or more. A relatively long follow-up with a minimal loss to follow-up allowed analysis on long-term complications, delayed recurrent bleeding and overall survival. Survival analyses are based on death certificates provided by Statistics Finland. Receiving reports on all deaths in the country, it produces accurate data and has coverage of nearly 100% in the cause of death statistics [146]. Despite single-center setting and relatively small study populations, Study I is the largest published cohort of patients undergoing the non-surgical management of bleeding pancreatic pseudoaneurysms by combining arterial embolization and therapeutic endoscopy.

Studies I, II and IV are retrospective studies without control groups. Study II is a retrospective case-control study with historical controls and no randomization. As such, all four studies bear the weaknesses inherent to
retrospective single-center studies. Their fairly small study populations may also leave true statistical associations undetected, making the studies vulnerable to type II error.

6.5 FUTURE PROSPECTS

Interventional radiology is a continuously evolving field in terms of imaging methods and instrumentation. For the time being, the most common cause for failing arterial embolization is negative angiography. How improving techniques will overcome the issue in the future remains to be seen.

Clinical guidelines on TAE in UGIB are based on retrospective case-control studies. Randomized controlled trials comparing TAE and surgery do not exist. Due to its recent suspension, a multi-center randomized trial recruiting in Hong Kong since 2008 failed to put an end to the discussion concerning TAE and surgery in UGIB (ClinicalTrials.gov study identifier: NCT00766961). Slow patient accrual will be a major problem even in a multicentre study design, and it looks like TAE has established its role as the preferred treatment method over surgery after failed endoscopy without validation in a randomized trial.

Ischemia remains a concern especially in splenic artery embolization and in embolizations for LGIB. Arterial embolization literally means the deliberate occlusion of arterial blood flow. Despite super-selective technique and evolving instrumentation, ischemic complications will always remain a disadvantage inherent to the method.

6.6 GENERAL ASPECTS

Embolizing gastrointestinal bleeding is increasingly common. Despite this, the mainstay of treatment is always the stabilization and fluid resuscitation of the patient. The majority of patients require no more than watchful waiting or therapeutic endoscopy. Only a small proportion will develop profuse bleeding necessitating further hemostatic interventions. Interventional management is multidisciplinary and increasingly individualized and patient-oriented. Despite evolving treatment methods, patients with gastrointestinal bleeding continue to express high morbidity and mortality showing that profuse bleeding per se is a severe physiological insult in patients that are often moribund and elderly. Such patients in particular are likely to benefit from arterial embolization that offers a less invasive alternative to surgery in most non-traumatic bleeding emergencies.
7 CONCLUSIONS

The main findings of the current series of studies allow the following conclusions:

When available, arterial embolization is a technically feasible method in patients with gastrointestinal bleeding of arterial origin and positive angiography.

I:
The non-surgical management of bleeding pancreatic pseudoaneurysms by combining arterial embolization and therapeutic endoscopy is safe and effective, and it should be the recommended treatment approach of bleeding pancreatic pseudoaneurysms. The optimal timing of therapeutic endoscopy is not clear.

II:
The 30-day rebleeding and mortality rates did not differ in patients receiving arterial embolization and surgery for upper gastrointestinal bleeding. With less post-operative complications, embolization should be the preferred hemostatic method over surgery when endoscopic treatment fails.

III:
Lower gastrointestinal bleeding is a major physiological insult in often elderly and moribund patients. Arterial embolization should be the first-line intervention over surgery in patients with hemodynamic instability, when endoscopic hemostasis fails or is not feasible, or when computerized tomography angiography shows small intestinal bleeding. Ischemic complications occur with a notable frequency and necessitate pre-operative patient counselling.

IV:
Arterial embolization is an effective method in controlling the bleeding in patients with spontaneous hepatic tumor hemorrhage. Underlying tumor etiology determines the prognosis that is poor especially in cirrhotic patients with hepatocellular carcinoma.
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Taina
REFERENCES


